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MEYLER'S Side Effects of Drugs

The International Encyclopedia of Adverse Drug Reactions and Interactions

Fifteenth Edition

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In this list the main contributors to the Encyclopedia are identified according to the original chapter material to which they made the most contribution. Most have contributed the relevant chapters in one or more editions of the *Side Effects of Drugs Annuals* 23-27 and/or the 14th edition of *Meyler's Side Effects of Drugs*. A few have contributed individual monographs to this edition.

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Foreword

My doctor is
A good doctor
He made me no
Iller than I was

Willem Hussem (The Netherlands) 1900–1974
Translation: Peter Raven

"*Primum non nocere*"—in the first place, do no harm—is often cited as one of the foundation stones of sound medical care, yet its origin is uncertain. Hippocrates? There are some who will tell you so;[1] but the phrase is not a part of the Hippocratic Oath, and the Father of Medicine wrote in any case in his native Greek.[2] It could be that the Latin phrase is from the Roman physician Galenius, while others attribute it to Scribonius Largus, physician to one of the later Caesars,[3] and there is a lot of reason to believe that it actually originated in 19th century England.[4] Hippocrates himself, in the first volume of his *Epidemics*, put it at all events better in context: "When dealing with diseases have two precepts in mind: to procure benefit and not to harm."[5] One must not become overly obsessed by the safety issue, but it is a necessary element in good medical care.

The ability to do good with the help of medicines has developed immensely within the last century, but with it has come the need to keep a watchful eye on the possibility of inflicting harm on the way. The challenge is to recognize at the earliest possible stage the adverse effects that a valuable drug may induce, and to find ways of containing them, so that risk never becomes disproportionate to benefit. The process of drug development will sometimes result in methods of treatment that are more specific to their purpose than were their predecessors and hence less likely to produce unwanted complications; yet the more novel a therapeutic advance the greater the possibility of its eliciting adverse effects of a type so unfamiliar that they are not specifically looked for and long remained unrecognized when they do occur. The entire process of keeping medicines safe today involves all those concerned with them, whether as researchers, manufacturers, regulators, prescribers, dispensers, or users, and it demands an effective and honest flow of information and thought between them.

For several decennia, concerned by its own errors in the past, the science of therapeutics put unbounded faith in the ability of well-planned clinical trials to arrive at the truth about the properties of medicines. Insofar as efficacy was concerned that was and remains a sound move, closing the door to charlatanism as well as to well-meant amateurism. Therapeutic trials with a new medicine were also able to delineate those adverse effects that occurred in a fair proportion of users. If serious, they would bar the drug from entry to the market altogether, while if transient and reasonably tolerable they would form the basis for warnings and precautions as well as the occasional contraindication. The problem lay with those adverse drug reactions that occurred rather less commonly or not at all in populations recruited for therapeutic trials, yet which could soon arise in the much broader spectrum of patients exposed to the drug once it was marketed across the world. The influence of race or climate might explain some of them; others might reflect interactions with foods, alcohol, or other drugs; yet others could only be explained, if at all, in terms of the particular susceptibility of certain individuals. Scattered across the globe, these effects might readily be overlooked, regarded as coincidental, or at worst dismissed contemptuously as "merely anecdotal".

The seriousness of the adverse effects issue became very apparent even as the reputation of controlled trials deservedly grew, and it touched on both newer and older drugs. The thalidomide calamity, involving several thousand cases of drug-induced phocomelia, was fortunately recognized by Widukind Lenz and others in the light of individual case reports within two years of the introduction of the product. On the other hand, generations elapsed between the patenting of aspirin in 1899 and the realization in 1965 that it might induce Reye's syndrome when used to treat fever in children. Such events, and many less spectacular, showed that, however vital well-controlled studies had become, there was good reason to remain alert for signals emerging from individual cases. Unanticipated events occurring during drug treatment might indeed reflect mere coincidence, but again they might not; and for many of the patients who suffered in consequence there was nothing in the least anecdotal about them.

Fortunately, the 1950s and 1960s of the 20th century saw the first positive reactions to the adverse reaction issue. Effective drug regulation emerged in one country after another. In 1952, Prof. Leo Meyler of The Netherlands produced his first "Side Effect of Drugs" to pull together data from the world literature. A number of national adverse reaction monitoring bureaux were established to gather data from the field and examine carefully reports of suspected side effects of medicines, creating the basis for the World Health Organization to establish its global reporting system. The pharmaceutical industry has increasingly realized its duty to collect and pass on the information that comes into its possession through its wide contacts with the health professions. Later years have seen the emergence, notably in Sweden and in Britain, of systems through which patients themselves can report possible adverse effects to the medicines they have taken. All these processes fit together in what the French language so appropriately terms "pharmacovigilance", with vigilance as the watchword for all concerned.

In this continuing development, the medical literature provides a resource with vast potential. The world is believed to have some 20 000 medical journals, of which a nuclear group of a thousand or so can be relied upon to publish reports and analyses of adverse effects—not only in the framework of formal investigations but also in letters, editorials, and reports of meetings large and small. Much of that information comprises not so much firm facts as emergent knowledge, based directly on experience in the field and calling urgently for attention. The book that Leo Meyler created has, in the course of fifteen editions and with the support of an ever-larger team of professionals, provided the means by which that attention can be mobilized. It has become the world's principal tool in bringing together, encyclopedically but critically, the evidence on the basis of which adverse drug effects and interactions can be recognized, discussed, and accommodated into medical practice. Together with its massive database and its complementary *Side Effects of Drugs Annuals*, it has evolved into a vital instrument in ensuring that drugs are used wisely and well and with due caution, in the light of all that is known about them. There is nothing else like it, nor need there be; across the world, *Meyler* has become a pillar of responsible medical care.

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Notes

1. Lichtenhaeler C. Histoire de la Médicine, Fayard, Paris, 1978:117.
2. Smith CM. Origin and uses of *Primum non nocere*. J Clin Pharmacol 2005;45:371–7.
3. Albrecht H. Primum nil nocere. Die Zeit, 6 April, 2005.
4. Notably in a book by Inman T. *Foundation for a New Theory and Practice of Medicine*. London, 1860.
5. I am indebted to Jeffrey Aronson for his own translation of the Greek original from Hippocrates *Epidemics*, Book I, Section XI, which seems to convey the meaning of the original [ἀσκεῖν περὶ τὰ νοσημάτα δῦο, ὠφελειν ἢ μὴ βλάπτειν] rather better than the published translations of his work.

Preface

This is a completely new edition of what has become the standard reference text in the field of adverse drug reactions and interactions since Leopold Meyler published his first review of the subject 55 years ago. Although we have retained the old title, *Meyler's Side Effects of Drugs*, the subtitle of this edition, *The Encyclopedia of Adverse Drug Reactions and Interactions*, reflects both modern terminology and the scope of the review. The structure of the book may have changed, but the *Encyclopedia* remains the most comprehensive reference source on adverse drug reactions and interactions and a major source of informed discussion about them.

Scope

The scope of the *Encyclopedia* remains wide. It covers not only the vast majority of prescription drugs, old and new, but also non-prescribed substances (such as anesthetics, antiseptics, lifestyle compounds, and drugs of abuse), herbal medicines, devices (such as blood glucose meters), and methods in alternative and complementary medicine. For this edition, entries on some substances that were regarded as obsolete, such as thalidomide and smallpox vaccine, have been rewritten and restored. Other compounds, such as diethylstilbestrol, although no longer in use, continue to cast their shadow and are included. Yet others, currently regarded as obsolete, have been retained, both for historical reasons and because one can never be sure when an old compound may once more become relevant or provide useful information in relation to another compound. Some drugs have been withdrawn from the market in some countries since the last edition of *Meyler* was published; rofecoxib, cisapride, phenylpropanolamine, and kava (see Piperaceae) are examples. Nevertheless, detailed monographs have been included on these substances because of the lessons that they can teach us and in some cases because of their relevance to other compounds in their classes that are still available; it is also not possible to predict whether these compounds will eventually reappear in some other form or for some new indication.

In the last 15 years there has been increasing emphasis on the use of high-quality evidence in therapeutic practice, principally as obtained from large, randomized clinical trials and from systematic reviews of the results of many such trials. However, while it has been possible to obtain useful information about the beneficial effects of interventions in this way, evidence about harms, including adverse drug reactions, has been more difficult to obtain. Even trials that yield good estimates of benefits are poor at providing evidence about harms for several reasons:

- benefits are usually single, whereas harms are usually multiple;
- the chance of any single form of harm is usually smaller than the chance of benefit and therefore more difficult to detect; however, multiple harms can accumulate and affect the benefit-to-harm balance;
- benefits are identifiable in advance, whereas harms are not or not always;
- the likely time-course of benefits can generally be predicted, while the time-course of harms often cannot and may be much delayed by comparison with the duration of a trial.

For all these reasons, larger and sometimes longer studies are needed to detect harms. In recent years attempts have been made to conduct systematic reviews of adverse reactions, but these have also been limited by several problems:

- harms are in general poorly collected in randomized trials and trials may not last long enough to detect them all;
- even when they are well collected, as is increasingly happening, they are often poorly reported;
- even when they are well reported in the body of a report, they may not be mentioned in titles and abstracts;
- even when they are well reported in the body of a report, they may be poorly indexed in large databases.

All this means that it is difficult to collect information on adverse drug reactions from randomized, controlled trials for systematic review. This can be seen from the evidence provided in Table 1, which shows the proportion of different types of information that have been used in the preparation of two volumes of the *Side Effects of Drugs Annual*, proportions that are likely be the same in this *Encyclopedia*.

Wherever possible, emphasis in this *Encyclopedia* has been placed on information that has come from systematic reviews and clinical trials of all kinds; this is reflected in new headings under which trial results are reported (observational studies, randomized studies, placebo-controlled studies). However, because many reports of adverse drug reactions (about 30%) are anecdotal, with evidence from one or just a few cases, many individual case studies (see below) have also been included. We need better methods to make use of the information that this large body of anecdotes provides.

Structure

The first major change that readers will notice is that the chapter structure of previous editions has given way to a monographic structure. That is because some of the information about individual drugs has previously been scattered over different chapters in the book; for example ciclosporin was previously covered in Chapter 37 and in scattered sections throughout Chapter 45; it is now dealt with in a single monograph. The monographs are arranged in alphabetical order, with cross-referencing as required. For example, if you turn to the monograph on cetirizine, you will be referred to the complementary general monograph on antihistamines, where much information that is relevant to cetirizine is given; the monograph on cetirizine itself contains information that is relevant only to cetirizine and not to other antihistamines. Within each monograph the material is arranged in the same way as in the *Side Effects of Drugs Annuals* (see "How to use this book").

Case Reports

A new feature, recognizable from the Annuals, but not incorporated into previous editions, is the inclusion of case reports of adverse effects. This feature reflects the fact that about 30% of all the literature that is reported and discussed in the Annuals derives from such reports (see Table 1). In some cases the only information about an adverse effect is contained in an anecdotal report; in other cases the report illustrates a variant form of the reaction. A case report also gives more immediacy to an adverse reaction, allowing the reader to appreciate more precisely the exact nature of the reported event.

Classification of Adverse Drug Reactions

Another new feature of this edition is the introduction of the DoTS method of classifying adverse drug reactions, based on the **Dose** at which they occur relative to the beneficial dose, the **Time-course** of the reaction, and individual **Susceptibility factors** (see "How to use this book"). This has been done for selected adverse effects, and I hope that as volumes of SEDA continue to be published and the *Encyclopedia's* electronic database is expanded, it will be possible to classify increasing numbers of adverse reactions in this way.

References

Because all the primary and secondary literature is thoroughly surveyed in the Annuals, the *Encyclopedia* has become increasingly compact relative to the amount of information available (even though it has increased in absolute size), with many unreferenced statements and cross-references to the Annuals, on the assumption that all the information would be readily available to the reader, although that may not always be the case. To restore all the reference material on which the *Encyclopedia* has been based as it has evolved over so many years would be a gargantuan task, but in this edition a major start has been made. Many references to original material have been restored, and there is now hardly a statement that is not backed up by at least one reference to primary literature. In addition, almost all of the material that was published in Annuals 23 to 27 (SEDA-23 to SEDA-27) has been included, complete with citations. This has resulted in the inclusion of more than 40 000 references in this edition. Readers will still have to refer to earlier editions of the Annual (SEDA-1 to SEDA-22) and occasionally to earlier editions of *Meyler's Side Effects of Drugs* for more detailed descriptions, but now that the *Encyclopedia* is available electronically this will be repaired in future editions.

Methods and Contributors

I initially prepared the text of the *Encyclopedia* by combining text from the 14th edition of *Meyler's Side Effects of Drugs* and the five most recent annuals (SEDA-23 to SEDA-27). [Later literature is covered in SEDA-28 and the forthcoming SEDA-29.] I next restored missing references to the material and extended it where important information had not been included. The resulting monographs were then sent to experts for review, and their comments were incorporated into the finished monographs. I am grateful to all those, both authors of chapters in previous editions and Annuals and those who have reviewed the monographs for this edition, for their hard work and for making their expertise available.

Acknowledgements

This 15th edition of *Meyler's Side Effects of Drugs* was initiated and carefully planned with Joke Jaarsma at Elsevier, who has provided unstinting support during the production of several previous editions of *Meyler's Side Effects of Drugs* and the *Side Effects of Drugs Annuals*. Early discussions with Dieke van Wijnen at Elsevier about the structure of the text were invaluable. Professor Leufkens from the Faculty of Pharmacy at the University of Utrecht was instrumental in helping us to assemble the preliminary content for this edition; pharmacy students in his department entered the text

Table 1 Types of articles on adverse drug reactions published in 6576 papers in the world literature during 1999 and 2003 (as reviewed in SEDA-24 and SEDA-28)

Type of article	Number of descriptions* (%)
An anecdote or set of anecdotes (that is reported case histories)	2084 (29.9)
A major, randomized, controlled trial or observational study	1956 (28.1)
A minor, randomized, controlled trial or observational study or a non-randomized study (including case series)	1099 (15.8)
A major review, including non-systematic statistical analyses of published studies	951 (13.7)
A brief commentary (for example an editorial or a letter)	362 (5.19)
An experimental study (animal or in vitro)	263 (3.77)
A meta-analysis or other form of systematic review	172 (2.47)
Official statements (for example by Governmental organizations, the WHO, or manufacturers)	75 (1.07)
Total no. of descriptions*	6962
Total no. of articles	6576

* Some articles are described in more than one way

electronically into templates under the guidance of Joke Zwetsloot from Elsevier. Christine Ayorinde provided excellent assistance while I expanded and edited the material. The International Non-proprietary Names were checked by Renée Aronson. At Elsevier the references were then checked and collated by Liz Perill, who also copyedited the material, with Ed Stolting, and shepherded it through conversion to different electronic formats. Bill Todd created the indexes. Stephanie Diment oversaw the project and coordinated everyone's efforts.

The History of Meyler

The history of *Meyler's Side Effects of Drugs* goes back 55 years; a full account can be found at http://www.elsevier.-com/locate/Meyler and the various volumes are listed before the title page of this set. When Leopold Meyler, a physician, experienced unwanted effects of drugs that were used to treat his tuberculosis, he discovered that there was no single text to which medical practitioners could turn for information about the adverse effects of drug therapy; Louis Lewin's text *Die Nebenwirkungen der Arzneimittel* ("The Untoward Effects of Drugs") of 1881 had long been out of print (SEDA-27, xxv–xxix). Meyler therefore surveyed the current literature, initially in Dutch as *Schadelijke Nevenwerkingen van Geneesmiddelen* (Van Gorcum, 1951), and then in English as *Side Effects of Drugs* (Elsevier, 1952). He followed up with what he called surveys of unwanted effects of drugs. Each survey covered a period of two to four years and culminated in Volume VIII (1976), edited by Graham Dukes (SEDA-23, xxiii-xxvi), Meyler having died in 1973. By then the published literature was too extensive to be comfortably encompassed in a four-yearly cycle, and an annual cycle was started instead; the first *Side Effects of Drugs Annual* (SEDA-1) was published in 1977. The four-yearly review was replaced by a complementary critical encyclopaedic survey of the entire field; the first encyclopaedic edition of *Meyler's Side Effects of Drugs*, which appeared in 1980, was labeled the ninth edition.

Since then, *Meyler's Side Effects of Drugs* has been published every four years, providing an encyclopaedic survey of the entire field. Had the cycle been adhered to, the 15th edition would have been published in 2004, but over successive editions the quantity and nature of the information available in the text has changed. In the new millennium it was clear that for this edition a revolutionary approach was needed, and that has taken a little longer to achieve, with a great deal of effort from many different individuals.

We have come a long way since Meyler published his first account in a book of 192 pages. I think that he would have approved of this new *Encyclopedia*.

Jeffrey K. Aronson
Oxford, October 2005

Using the Encyclopedia

In a departure from its previous structure, this edition of *Meyler's Side Effects of Drugs* is presented as individual drug monographs in alphabetical order. In many cases a general monograph (for example Antihistamines) is complemented by monographs about specific drugs (for example acrivastine, antazoline, etc.); in that case a cross-reference is given from the latter to the former.

Monograph Structure

Within each monograph the information is presented in sections as follows:

GENERAL INFORMATION
Includes, when necessary, notes on nomenclature, information about the results of observational studies, comparative studies, and placebo-controlled studies in relation to reports of adverse drug reactions, and a general summary of the major adverse effects.

ORGANS AND SYSTEMS
- Cardiovascular (includes heart and blood vessels)
- Respiratory
- Ear, nose, throat
- Nervous system (includes central and peripheral nervous systems)
- Neuromuscular function
- Sensory systems (includes eyes, ears, taste)
- Psychological, psychiatric
- Endocrine (includes hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, sex hormones)
- Metabolism
- Nutrition (includes effects on amino acids, essential fatty acids, vitamins, micronutrients)
- Electrolyte balance (includes sodium, potassium)
- Mineral balance (includes calcium, phosphate)
- Metal metabolism (includes copper, iron, magnesium, zinc)
- Acid–base balance
- Fluid balance
- Hematologic (includes blood, spleen, and lymphatics)
- Mouth and teeth
- Salivary glands
- Gastrointestinal (includes esophagus, stomach, small bowel, large bowel)
- Liver
- Biliary tract
- Pancreas
- Urinary tract (includes kidneys, ureters, bladder, urethra)
- Skin
- Hair
- Nails
- Sweat glands
- Serosae (includes pleura, pericardium, peritoneum)
- Musculoskeletal (includes muscles, bones, joints)
- Sexual function
- Reproductive system (includes uterus, ovaries, breasts)
- Immunologic (includes effects on the immune system and hypersensitivity reactions)
- Autacoids
- Infection risk
- Body temperature
- Multiorgan failure
- Trauma
- Death

LONG-TERM EFFECTS
- Drug abuse
- Drug misuse
- Drug tolerance
- Drug resistance
- Drug dependence
- Drug withdrawal
- Genotoxicity
- Mutagenicity
- Tumorigenicity

SECOND-GENERATION EFFECTS
- Fertility
- Pregnancy
- Teratogenicity
- Fetotoxicity
- Lactation

SUSCEPTIBILITY FACTORS (relates to features of the patient)
- Genetic factors
- Age
- Sex
- Physiological factors
- Cardiac disease
- Renal disease
- Hepatic disease
- Thyroid disease
- Other features of the patient

DRUG ADMINISTRATION
- Drug formulations
- Drug additives
- Drug contamination (includes infective agents)
- Drug adulteration
- Drug dosage regimens (includes frequency and duration of administration)
- Drug administration route
- Drug overdose

DRUG–DRUG INTERACTIONS
FOOD–DRUG INTERACTIONS
SMOKING
OTHER ENVIRONMENTAL INTERACTIONS
INTERFERENCE WITH DIAGNOSTIC TESTS
DIAGNOSIS OF ADVERSE DRUG REACTIONS
MANAGEMENT OF ADVERSE DRUG REACTIONS
MONITORING THERAPY

Classification of Adverse Drug Reactions

Selected major reactions are classified according to the DoTS system (BMJ 2003;327:1222–5). In this system adverse reactions are classified according to the **Dose** at which they usually occur relative to the beneficial dose, the **Time-course** over which they occur, and the **Susceptibility factors** that make them more likely, as follows:

1 Relation to dose
- *Toxic reactions* (reactions that occur at supratherapeutic doses)
- *Collateral reactions* (reactions that occur at standard therapeutic doses)
- *Hypersusceptibility reactions* (reactions that occur at subtherapeutic doses in susceptible patients)

2 Time-course
- *Time-independent reactions* (reactions that occur at any time during a course of therapy)
- *Time-dependent reactions*
  - Immediate reactions (reactions that occur only when a drug is administered too rapidly)
  - First-dose reactions (reactions that occur after the first dose of a course of treatment and not necessarily thereafter)
  - Early reactions (reactions that occur early in treatment then abate with continuing treatment)
  - Intermediate reactions (reactions that occur after some delay but with less risk during longer- term therapy, owing to the "healthy survivor" effect)
  - Late reactions (reactions the risk of which increases with continued or repeated exposure), including withdrawal reactions (reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced)
  - Delayed reactions (reactions that occur some time after exposure, even if the drug is withdrawn before the reaction appears)

3 Susceptibility factors
- *Genetic*
- *Age*
- *Sex*
- *Physiological variation*
- *Exogenous factors* (for example drug–drug or food–drug interactions, smoking)
- *Diseases*

Drug Names And Spelling

Drugs are usually designated by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available, chemical names have been used. If a fixed combination has a generic combination name (for example co-trimoxazole for trimethoprim + sulfamethoxazole) that name has been used; in some cases brand names have been used.

Spelling

Where necessary, for indexing purposes, American spelling has been used, for example anemia rather than anaemia, estrogen rather than oestrogen.

Cross-references

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-l3, SED-14, etc.; the *Side Effects of Drugs Annuals* 1-22 are cited as SEDA-1, SEDA-2, etc. This edition includes most of the contents of SEDA-23 to SEDA-27. SEDA-28 and SEDA-29 are separate publications, which were prepared in parallel with the preparation of this edition.

Searching the online edition

The print edition of this Reference Work contains two indexes, the "Index of Drug Names" and the "Index of Adverse Reactions". Both indexes are print oriented and point at pages in the main text in which a reaction is discussed or a drug name used.

In the online environment these are redundant as free-standing indexes since on ScienceDirect simple searches can achieve the same results more efficiently and quickly. In addition, whilst the print "Index of Adverse Reactions" was necessarily selective no such constraint affects the online edition.

On ScienceDirect (and assuming you are subscribed to this Reference Work) you may use either the Basic Search Form or Advanced Search. For the purposes of simplicity in these notes only the Basic Search is described. (Quick Search is also supported but offers less granular options than the other search types.)

Familiarity with the structure of the monographs in the print encyclopedia can be used to advantage in targeting precise locations in the text. As with all other searches on ScienceDirect, the results are returned as article titles (including citation information) and (for Reference Works) in book order by default.

For example, to locate the article on "Venlafaxine" you can either navigate to it via clicking on the "Article Titles" browse tab and then on the letter "V" and scroll down to this entry.

Alternatively, on the Basic Search form you can enter the term "Venlafaxine" in the search box and run the search against the "Article Titles" index. By default a search is run across "All Fields" and each field that is separately searchable is listed in the "within" drop-down list.

To extend the search to find this term wherever it occurs in the encyclopedia then you should run this search against "Full Text". Such a search will generate a list of all monographs in which the term appears. To rank the results by relevance rather than alphabetically by monograph title, select the option "by relevance" in the drop down on the Search Results List.

As noted above consistency of structure in the encyclopedia is a huge benefit in the online environment. For example, to recover all articles in which "Fluid balance" is affected in some way by any drug then you should run a search on the term "Fluid balance" in the field "Subheadings". This will recover all drugs for which some impact on fluid balance has been recorded.

Abacavir

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Abacavir is a guanidine analogue that inhibits HIV reverse transcriptase. In vitro, its potency is similar to that of zidovudine, protease inhibitors, and dual nucleoside combinations. There is evidence that abacavir is effective in reducing viral load and increasing the CD4 count in HIV-infected patients. Viral resistance is not rapidly selected for, but cross-resistance has been shown to other analogues of cytosine and guanidine (didanosine, lamivudine, and zalcitabine).

Abacavir has good oral systemic availability and penetrates the nervous system. It does not interfere with drugs that are metabolized by liver microsomal cytochrome P450 (1). It has no other significant drug interactions and can be administered without food restrictions.

Observational studies

The effects of abacavir have been evaluated in a study in over 13 000 adults who no longer responded to commercially available treatment regimens (2). By month 2 of treatment with abacavir, plasma HIV-1 RNA concentrations fell by at least half a log unit in 31% of patients, and in 5.6% of the patients HIV-1 RNA concentrations fell to under 400 copies/ml. Serious drug-related adverse events were reported by 7.7% of patients. The most common were nausea, skin rash, diarrhea, malaise or fatigue, and fever. About 4.6% of patients had a hypersensitivity reaction that was possibly drug-related.

General adverse effects

The adverse effects of abacavir that have been most often observed in clinical trials are fatigue, nausea and vomiting, abdominal pain, diarrhea, headache, rash, and dyspepsia (3,4). Allergic reactions lead to withdrawal of therapy in about 3% of patients (5). These can be severe, and anaphylaxis has been reported after rechallenge in a patient with an apparent allergic reaction to abacavir (6). It is wise to avoid rechallenge when allergy is suspected (7). In one study nausea and vomiting occurred in 38–57% of patients, headache in 27–41%, malaise and fatigue in 28%, diarrhea in 18–23%, and weakness in 29% (8). There was also one case of agranulocytosis accompanied by a skin rash.

Organs and Systems

Nervous system

Vertigo has been attributed to abacavir (9).

- A 44-year-old African-American developed vertigo, tinnitus in both ears, headache behind the eyes, and left ear pain and hearing loss soon after starting to take abacavir, lamivudine, and stavudine. There was left-sided nystagmus and vestibular tests showed evidence of vestibular impairment. An MRI scan was normal. All the antiretroviral drugs were withdrawn and he improved. When lamivudine and stavudine were restarted, with nevirapine, the vertigo did not recur.

Metabolism

While abacavir has been associated with hyperglycemia in individual cases (10), there were no significant effects on blood glucose concentration in clinical trials.

- A 47-year-old man, with normoglycemia and no family history of diabetes mellitus, who was taking highly active antiretroviral therapy, was given abacavir for treatment intensification. He became lethargic and hyperglycemic. Despite metformin and glibenclamide, the hyperglycemia continued. Abacavir was withdrawn, and within 2 weeks his blood glucose concentration returned to baseline and the hypoglycemic drugs were withdrawn.

This patient was also taking hydrochlorothiazide, but the time-course of onset and resolution were consistent with abacavir-induced hyperglycemia.

Immunologic

The risk of allergic reactions to abacavir may be as high as 10% (11). However, the incidence is more usually reported to be 3–5% (12,13). Allergic reactions usually occur within the first 28 days of therapy and rarely thereafter. They are characterized by non-specific complaints suggestive of an upper respiratory tract infection, fever, rash, nausea, and vomiting. Resolution of the symptoms occurs within days of withdrawal. Severe and even fatal reactions to readministration have been observed, and it has been suggested that rechallenge is contraindicated in any patients who have had an allergic reaction (7). However, it is safe to rechallenge patients who have stopped treatment because of other types of adverse reaction. Of 1201 patients treated in clinical trials, 219 interrupted abacavir therapy for reasons other than allergy; on reintroduction there were no cases of allergy or anaphylaxis (14).

The susceptibility factors associated with allergic reactions have been sought in an analysis of all protocols conducted by GlaxoSmithKline that involved abacavir exposure for at least 24 weeks with a quality-assured or validated clinical database by 30 June 2000 ($n = 5332$) (15). There were 197 allergic reactions (3.7%). The risks of allergic reactions were lower in black people (OR = 0.59; 95% CI = 0.38, 0.91) than in other ethnic groups, and in patients who had received previous therapy for HIV-1 infection with other antiretroviral agents (OR = 0.58; 95% CI = 0.44, 0.78) compared with those receiving therapy for the first time.

Genetic factors affecting the immune response to abacavir have been sought in patients who had taken abacavir for more than 6 weeks, 18 with hypersensitivity reactions and 167 without (16). HLA-B*5701 was present in 14 of the 18 patients with abacavir hypersensitivity, and in four of the 167 others (OR = 117; 95% CI = 29, 481). The combination of HLA-DR7 and

HLA-DQ3 was found in 13 of the 18 and five of the 167 (OR = 73; CI = 20, 268). HLA-B*5701, HLA-DR7, and HLA-DQ3 were present in combination in 13 of the 18 and none of the 167 (OR = 822; CI = 43, 15 675). Other MHC markers also present on the 57.1 ancestral haplotype to which these three markers belong confirmed the presence of haplotype-specific linkage disequilibrium, and mapped potential susceptibility loci to a region bounded by C4A6 and HLA-C. HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%. The authors concluded that susceptibility to abacavir hypersensitivity is carried on the 57.1 ancestral haplotype and that withholding abacavir from those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2.5% without inappropriately denying abacavir to any patient.

In a retrospective case-control study of patients with allergic reactions, HLA-B57 was present in 39 of 84 patients compared with 4 of 113 controls (17). However, there were few women and other ethnic groups in the study, and so these findings relate largely to white men.

In a multicenter trial, 128 children were randomly assigned to zidovudine + lamivudine ($n = 36$), to zidovudine + abacavir ($n = 45$), or to lamivudine + abacavir ($n = 47$) (18). One child had an allergic reaction to abacavir and stopped taking it, as did three with possible reactions.

References

1. Ravitch JR, Bryant BJ, Reese MJ, et al. In vivo and in vitro studies of the potential for drug interactions involving the anti-retroviral 1592 in humans. 5th Conference on Retroviruses and Opportunistic Infections, Chicago, 1–5 February 1998: Abstract 634.
2. Kessler HA, Johnson J, Follansbee S, Sension MG, Mildvan D, Sepulveda GE, Bellos NC, Hetherington SV. Abacavir expanded access program for adult patients infected with human immunodeficiency virus type 1. Clin Infect Dis 2002;34(4):535–42.
3. Kumar PN, Sweet DE, McDowell JA, Symonds W, Lou Y, Hetherington S, LaFon S. Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. Antimicrob Agents Chemother 1999;43(3):603–8.
4. Vernazza PL, Katlama C, Clotet B, et al. Intensification of stable background (SBG) antiretroviral therapy (ART) with Ziagen (ABC,1592). 6th Conference on Retroviruses and Opportunistic Infections, Chicago, Jan 31–Feb 4 1999.
5. Staszewski S. Coming therapies: abacavir. Int J Clin Pract Suppl 1999;103:35–8.
6. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. AIDS 1999;13(8):999–1000.
7. Escaut L, Liotier JY, Albengres E, Cheminot N, Vittecoq D. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS 1999;13(11):1419–20.
8. Tikhomirov V, Namek K, Hindes R. Agranulocytosis induced by abacavir. AIDS 1999;13(11):1420–1.
9. Fantry LE, Staecker H. Vertigo and abacavir. AIDS Patient Care STDS 2002;16(1):5–7.
10. Modest GA, Fuller J, Hetherington SV, Lenhard JM, Powell GS. Abacavir and diabetes. N Engl J Med 2001;344(2):142–4.
11. Katlama C, Fenske S, Gazzard B, Lazzarin A, Clumeck N, Mallolas J, Lafeuillade A, Mamet JP, Beauvais L; AZL30002 European study team. TRIZAL study: switching from successful HAART to Trizivir (abacavir–lamivudine–zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. HIV Med 2003;4(2):79–86.
12. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. Drugs 2000;60(2):447–79.
13. Henry K, Wallace RJ, Bellman PC, Norris D, Fisher RL, Ross LL, Liao Q, Shaefer MS; TARGET Study Team. Twice-daily triple nucleoside intensification treatment with lamivudine–zidovudine plus abacavir sustains suppression of human immunodeficiency virus type 1: results of the TARGET Study. J Infect Dis 2001;183(4):571–8.
14. Loeliger AE, Steel H, McGuirk S, Powell WS, Hetherington SV. The abacavir hypersensitivity reaction and interruptions in therapy. AIDS 2001;15(10):1325–6.
15. Symonds W, Cutrell A, Edwards M, Steel H, Spreen B, Powell G, McGuirk S, Hetherington S. Risk factor analysis of hypersensitivity reactions to abacavir. Clin Ther 2002;24(4):565–73.
16. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002;359(9308):727–32.
17. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359(9312):1121–2.
18. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet 2002;359(9308):733–40.

Abciximab

See also Monoclonal antibodies

General Information

Abciximab is a Fab fragment of the chimeric human-murine monoclonal antibody 7E3, which binds to the platelet glycoprotein IIb/IIIa receptor and inhibits platelet aggregation (1).

Abciximab is used for prevention of cardiac ischemic events in patients undergoing percutaneous coronary intervention and to prevent myocardial infarction in patients with unstable angina who do not respond to conventional treatment. It has also been used for thrombolysis in patients with peripheral arterial occlusive disease and arterial thrombosis (2).

Besides bleeding, other adverse reactions that have been associated with abciximab include back pain,

HLA-DQ3 was found in 13 of the 18 and five of the 167 (OR = 73; CI = 20, 268). HLA-B*5701, HLA-DR7, and HLA-DQ3 were present in combination in 13 of the 18 and none of the 167 (OR = 822; CI = 43, 15 675). Other MHC markers also present on the 57.1 ancestral haplotype to which these three markers belong confirmed the presence of haplotype-specific linkage disequilibrium, and mapped potential susceptibility loci to a region bounded by C4A6 and HLA-C. HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%. The authors concluded that susceptibility to abacavir hypersensitivity is carried on the 57.1 ancestral haplotype and that withholding abacavir from those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2.5% without inappropriately denying abacavir to any patient.

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References

1. Ravitch JR, Bryant BJ, Reese MJ, et al. In vivo and in vitro studies of the potential for drug interactions involving the anti-retroviral 1592 in humans. 5th Conference on Retroviruses and Opportunistic Infections, Chicago, 1–5 February 1998: Abstract 634.
2. Kessler HA, Johnson J, Follansbee S, Sension MG, Mildvan D, Sepulveda GE, Bellos NC, Hetherington SV. Abacavir expanded access program for adult patients infected with human immunodeficiency virus type 1. Clin Infect Dis 2002;34(4):535–42.
3. Kumar PN, Sweet DE, McDowell JA, Symonds W, Lou Y, Hetherington S, LaFon S. Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. Antimicrob Agents Chemother 1999;43(3):603–8.
4. Vernazza PL, Katlama C, Clotet B, et al. Intensification of stable background (SBG) antiretroviral therapy (ART) with Ziagen (ABC,1592). 6th Conference on Retroviruses and Opportunistic Infections, Chicago, Jan 31–Feb 4 1999.
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17. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359(9312):1121–2.
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Besides bleeding, other adverse reactions that have been associated with abciximab include back pain,

hypotension, nausea, and chest pain (but with an incidence not significantly different from that observed with placebo).

Organs and Systems

Respiratory

Lung hemorrhage is a rare but potentially lethal complication of antithrombotic and antiplatelet therapy. The incidence of spontaneous pulmonary hemorrhage after the use of platelet glycoprotein IIb/IIIa inhibitors has been analysed from the medical records of 1020 consecutive patients who underwent coronary interventions (3). Diffuse pulmonary hemorrhage developed in seven patients, two of whom died and five of whom had activated clotting times greater than 250 seconds during the procedure. Activated partial thromboplastin time measured at the time of lung hemorrhage was raised in all cases (mean 85, range 69–95 seconds). All had a history of congestive heart failure, and had raised pulmonary capillary wedge pressures and/or left ventricular end-diastolic pressures at the time of the procedure. Six patients also had evidence of baseline radiographic abnormalities.

Nervous system

Seven patients undergoing neurointerventional procedures who received abciximab developed fatal intracerebral hemorrhages (4). The procedures included angioplasty and stent placement in the cervical internal carotid artery ($n = 4$), angioplasty of the intracranial carotid artery ($n = 1$), and angioplasty of the middle cerebral artery ($n = 2$). Aggressive antithrombotic treatment is used as adjuvant to angioplasty and/or stent placement to reduce the rate of ischemic and thrombotic complications associated with these procedures. Intravenous abciximab has a short life (10 minutes), but its inhibitory effect on platelets lasts for 48 hours. The exact cause of abciximab-associated intracerebral hemorrhage is unclear.

Hematologic

Bleeding

The primary risk associated with abciximab is bleeding. In the EPIC trial in high-risk angioplasty, 14% of patients who received a bolus of abciximab followed by an infusion had a major bleeding complication rate, versus 7% in the placebo group (5). The most marked excess of major bleeding episodes occurred at the site of vascular puncture, but there were also a substantial number of gastrointestinal haemorrhages. However, the therapeutic regimen used was not adjusted for body weight, and the risk of major bleeding was also related to the heparin dose per kg and not only to the use of abciximab (6).

In 7800 patients with chest pain and either ST segment depression or a positive troponin test, the addition of abciximab to unfractionated heparin or low molecular weight heparin in the treatment of acute coronary syndrome was not associated with any significant reduction in cardiac events, but a doubled risk of bleeding (7).

An analysis of data from the EPIC trial identified a series of factors that predicted vascular access site bleeding or the need for vascular access site surgery in abciximab-treated patients (8). They comprised larger vascular access sheath size, the presence of acute myocardial infarction at enrolment, female sex, higher baseline hematocrits, lower body weight, and a longer time spent in the catheterization laboratory.

It must be emphasized that patients in the EPIC trial received high-dose heparin and that vascular access site sheaths were left in place for 12–16 hours. In subsequent studies, the risk of vascular site bleeding was probably reduced by using lower doses of heparin and removing sheaths sooner. This was the case in the EPILOG trial in which heparin was withdrawn immediately after the coronary procedure and vascular sheaths were removed as soon as possible (9). The incidence of major bleeding in this study was not significantly higher with abciximab than with placebo. Nevertheless, the incidence of minor bleeding complications was significantly higher in the abciximab plus standard dose heparin group (but not in the abciximab plus low dose heparin group) compared with placebo. In the EPISTENT trial, all patients received low dose, body weight-adjusted heparin: Here the incidence of both major and minor bleeding complications was low and not significantly different between treatment groups (10).

It would therefore seem possible to reduce the incidence of bleeding complications when using abciximab during prophylactic coronary revascularization procedures. This is unfortunately not the case so far in the setting of primary angioplasty for myocardial infarction after intense anticoagulation (17% of major hemorrhagic complications versus 9.5 in placebo recipients) (11). The risk of serious bleeding complications is also increased in rescue situations when high doses of heparin have been used (12), but here it can be reduced by giving protamine to reverse heparin anticoagulation before abciximab therapy (13). There is also a high incidence of major bleeding in patients who receive abciximab during percutaneous coronary revascularization after unsuccessful thrombolytic therapy. It has been suggested that abciximab should not be administered within 18 hours after thrombolytic therapy (14).

It must be emphasized that very few episodes of abciximab-related bleeding are life-threatening and that in none of the trials with abciximab as well as with other glycoprotein IIb/IIIa antagonists has there been an excess of intracranial hemorrhage (15).

However, the bleeding risk in patients enrolled in trials may not be representative of the population actually being given abciximab. To clarify this, a review of adverse events in patients receiving glycoprotein IIb/IIIa inhibitors reported to the FDA has been undertaken (16,17). The FDA received 450 reports of deaths related to treatment with glycoprotein IIb/IIIa inhibitors between November 1, 1997 and December 31, 2000; these were reviewed and a standard rating system for assessing causation was applied to each event. Of the 450 deaths, 44% were considered to be definitely or probably attributable to glycoprotein IIb/IIIa inhibitors.

The mean age of patients who died was 69 years and 47% of the deaths were in women. All of the deaths that were deemed to be definitely or probably associated with glycoprotein IIb/IIIa inhibitors were associated with excessive bleeding, most often in the nervous system.

Thrombocytopenia

The other significant risk associated with abciximab is thrombocytopenia. Data pooled from three major trials showed that thrombocytopenia (under 100×10^9/l) was significantly more frequent in those who received a bolus dose of abciximab followed by an infusion than in placebo recipients (3.7 versus 2%). Severe thrombocytopenia (under 50×10^9/l) was also more frequent with abciximab (1.1 versus 0.5%) (18). Very acute and profound thrombocytopenia (under 20×10^9/l) within 24 hours after administration has been observed in 0.3–0.7% of patients treated with abciximab for the first time (15,18–20).

During postmarketing surveillance of the first 4000 patients treated with abciximab in France, 25 cases of thrombocytopenia (0.6%) were reported, with five severe cases (0.15%) and three acute profound forms (0.08%). In all cases reported, the role of heparin must be taken into account. The thrombocytopenia associated with abciximab differs with that associated with heparin by its rapid onset (within 24 hours), its reversal after platelet transfusion, and its possible association with hemorrhage but not with thrombosis.

Positive human anti-chimeric antibodies have been detected in 6% of patients (generally in low titers) but were not associated with hypersensitivity or allergic reactions. Preliminary data indicate that abciximab can be safety readministered, although a greater incidence of thrombocytopenia after administration has been reported with a lesser efficacy of platelet transfusion (12).

Thrombocytopenia due to abciximab usually occurs within 12–96 hours, but there has been a report of acute profound thrombocytopenia after 7 days (21).

- A 65-year-old woman with type 2 diabetes mellitus and coronary artery disease received a 0.25 mg/kg bolus of abciximab at the time of intervention followed by an infusion of 10 micrograms/minute for 12 hours. Her baseline platelet counts were 286×10^9/l before use, 385×10^9/l at 2 hours, and 296×10^9/l at 18 hours. On day 7 she developed petechiae over her legs and her platelet count was 1×10^9/l. Coagulation tests were normal and there was no evidence of heparin-induced thrombocytopenia. She received 10 units of single-donor platelets and recovered slowly over the next 4 days. The platelet count was 114×10^9/l on day 12.

In another case of profound thrombocytopenia after abciximab there was a delayed onset (6 days after therapy) (22). The authors speculated that preceding treatment with methylprednisolone may have delayed the onset of thrombocytopenia.The mechanism of severe thrombocytopenia associated with abciximab is unclear. Further administration should be avoided, but other glycoprotein IIb/IIIa inhibitors (eptifibatide and tirofiban) have been successfully used in patients with history of abciximab-induced thrombocytopenia.

Thrombocytopenia after a second exposure to abciximab in nine patients showed that each had a strong immunoglobulin IgG antibody that recognized platelets sensitized with abciximab (23). Five patients also had IgM antibodies. Thrombocytopenia occurred four times as often as after the first exposure. The mechanism is not understood, but these findings suggest that it may be antibody-mediated. These antibodies were also found in 77 of 104 healthy patients, but in the patients the antibodies were specific for murine sequences in abciximab, causing the life-threatening thrombocytopenia.

Nine patients who developed profound thrombocytopenia after a second exposure to abciximab had an IgG antibody that recognized platelets sensitized with abciximab. In contrast, in 104 healthy subjects, in whom IgG antibodies reactive with abciximab-coated platelets were found in 77, the antibodies were specific for murine sequences in abciximab and were capable of causing life-threatening thrombocytopenia (23).

Ethylenediaminetetra-acetate can cause pseudothrombocytopenia by activating platelet agglutination, resulting in a spuriously low platelet count (SEDA-21, 250). Of 66 patients who received abciximab after coronary revascularization, 17 developed thrombocytopenia and 9 developed severe thrombocytopenia (24). However, of these 26 patients, 18 had pseudothrombocytopenia. True thrombocytopenia occurred at 4 hours after infusion whereas pseudothrombocytopenia occurred within the first 24 hours. The mechanism of pseudothrombocytopenia may be the effect of EDTA on the calcium-dependant glycoprotein IIb/IIIa complex, which frees the antigenic binding site on glycoprotein IIb available to IgM antibody. This increased antibody binding may cause platelet clumping and lead to false thrombocytopenia. True thrombocytopenia did not lead to hemorrhagic complications, but the patients required platelet transfusion.

Immunologic

Human antichimeric antibodies, specific to the murine epitope of Fab antibody fragments, have been observed in patients treated with abciximab. These antibodies are IgG antibodies and have so far not correlated with any adverse effects (12).

Because of its antigenic potential, there are theoretical concerns about the readministration of abciximab, and this has been studied in 1342 patients, who underwent percutaneous coronary interventions and received abciximab at least twice (25). There were no cases of anaphylaxis, and there were only five minor allergic reactions, none of which required termination of the infusion. There was clinically significant bleeding in 31 patients, including one with intracranial hemorrhage. There was thrombocytopenia (platelet count below 100×10^9/l) in 5% and profound thrombocytopenia (platelet count below 20×10^9/l) in 2%. In patients who received abciximab within 1 month of a previous treatment ($n = 115$), the risks of thrombocytopenia and profound thrombocytopenia were 17 and 12% respectively. Human chimeric antibody titers before

readministration did not correlate with adverse outcomes or bleeding, but were associated with thrombocytopenia and profound thrombocytopenia.

An anaphylactic reaction to abciximab has been reported (26).

- An obese 46-year-old woman with prolonged angina pectoris underwent coronary angiography. She had no known drug allergies, but on administration of an iodinated contrast media she developed anaphylactic shock. After successful resuscitation angiography was completed and she was given aspirin, ticlopidine for a month, and metoprolol. Five months later she developed chest pain again, and angiography was repeated after pretreatment with prednisone and diphenhydramine and she was given abciximab. Within 5 minutes she had an anaphylactic reaction, requiring resuscitation.

This case shows that anaphylactic reactions to abciximab can occur even after pretreatment with prednisone and diphenhydramine for a known allergy to iodine.

Susceptibility Factors

Renal disease

The available data do not suggest an increased risk of bleeding with abciximab among patients with mild to moderate renal insufficiency (19), even though there is reduced platelet aggregation in renal insufficiency.

References

1. Ibbotson T, McGavin JK, Goa KL. Abciximab: an updated review of its therapeutic use in patients with ischaemic heart disease undergoing percutaneous coronary revascularisation. Drugs 2003;63(11):1121–63.
2. Schweizer J, Kirch W, Koch R, Muller A, Hellner G, Forkmann L. Use of abciximab and tirofiban in patients with peripheral arterial occlusive disease and arterial thrombosis. Angiology 2003;54(2):155–61.
3. Ali A, Hashem M, Rosman HS, Kazmouz G, Gardin JM, Schrieber TL. Use of platelet glycoprotein IIb/IIIa inhibitors and spontaneous pulmonary hemorrhage. J Invasive Cardiol 2003;15(4):186–8.
4. Qureshi AI, Saad M, Zaidat OO, Suarez JI, Alexander MJ, Fareed M, Suri K, Ali Z, Hopkins LN. Intracerebral hemorrhages associated with neurointerventional procedures using a combination of antithrombotic agents including abciximab. Stroke 2002;33(7):1916–19.
5. The EPIC Investigation. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330(14):956–61.
6. Aguirre FV, Topol EJ, Ferguson JJ, Anderson K, Blankenship JC, Heuser RR, Sigmon K, Taylor M, Gottlieb R, Hanovich G, et al. Bleeding complications with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. EPIC Investigators. Circulation 1995; 91(12):2882–90.
7. James S, Armstrong P, Califf R, Husted S, Kontny F, Niemminen M, Pfisterer M, Simoons ML, Wallentin L. Safety and efficacy of abciximab combined with dalteparin in treatment of acute coronary syndromes. Eur Heart J 2002;23(19):1538–45.
8. Blankenship JC, Hellkamp AS, Aguirre FV, Demko SL, Topol EJ, Califf RM. Vascular access site complications after percutaneous coronary intervention with abciximab in the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial. Am J Cardiol 1998;81(1):36–40.
9. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336(24):1689–96.
10. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998;352(9122): 87–92.
11. Brener SJ, Barr LA, Burchenal JE, Katz S, George BS, Jones AA, Cohen ED, Gainey PC, White HJ, Cheek HB, Moses JW, Moliterno DJ, Effron MB, Topol EJ. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. Circulation 1998;98(8): 734–41.
12. Ferguson JJ, Kereiakes DJ, Adgey AA, Fox KA, Hillegass WB Jr, Pfisterer M, Vassanelli C. Safe use of platelet GP IIb/IIIa inhibitors. Am Heart J 1998;135(4):S77–89.
13. Kereiakes DJ, Broderick TM, Whang DD, Anderson L, Fye D. Partial reversal of heparin anticoagulation by intravenous protamine in abciximab-treated patients undergoing percutaneous intervention. Am J Cardiol 1997;80(5):633–4.
14. Kleiman NS. A risk-benefit assessment of abciximab in angioplasty. Drug Saf 1999;20(1):43–57.
15. Pinton P. Thrombopénies sous abciximab dans le traitement des syndromes coronariens aigus par angioplastie. [Abciximab-induced thrombopenia during treatment of acute coronary syndromes by angioplasty.] Ann Cardiol Angeiol (Paris) 1998;47(5):351–8.
16. Brown DL. Deaths associated with platelet glycoprotein IIb/IIIa inhibitor treatment. Heart 2003;89(5):535–7.
17. McLenachan JM. Who would I not give IIb/IIIa inhibitors to during percutaneous coronary intervention? Heart 2003;89(5):477–8.
18. Berkowitz SD, Harrington RA, Rund MM, Tcheng JE. Acute profound thrombocytopenia after C7E3 Fab (abciximab) therapy. Circulation 1997;95(4):809–13.
19. Foster RH, Wiseman LR. Abciximab. An updated review of its use in ischaemic heart disease. Drugs 1998;56(4):629–65.
20. Joseph T, Marco J, Gregorini L. Acute profound thrombocytopenia after abciximab therapy during coronary angioplasty. Clin Cardiol 1998;21(11):851–2.
21. Sharma S, Bhambi B, Nyitray W, Sharma G, Shambaugh S, Antonescu A, Shukla P, Denny E. Delayed profound thrombocytopenia presenting 7 days after use of abciximab (ReoPro). J Cardiovasc Pharmacol Ther 2002;7(1):21–4.
22. Schwarz S, Schwab S, Steiner HH, Hacke W. Secondary hemorrhage after intraventricular fibrinolysis: a cautionary note: a report of two cases. Neurosurgery 1998;42(3): 659–63.
23. Curtis BR, Swyers J, Divgi A, McFarland JG, Aster RH. Thrombocytopenia after second exposure to abciximab is caused by antibodies that recognize abciximab-coated platelets. Blood 2002;99(6):2054–9.

24. Schell DA, Ganti AK, Levitt R, Potti A. Thrombocytopenia associated with c7E3 Fab (abciximab). Ann Hematol 2002;81(2):76–9.
25. Dery JP, Braden GA, Lincoff AM, Kereiakes DJ, Browne K, Little T, George BS, Sane DC, Cines DB, Effron MB, Mascelli MA, Langrall MA, Damaraju L, Barnathan ES, Tcheng JE; ReoPro Readministration Registry Investigators. Final results of the ReoPro readministration registry. Am J Cardiol 2004;93(8):979–84.
26. Pharand C, Palisaitis DA, Hamel D. Potential anaphylactic shock with abciximab readministration. Pharmacotherapy 2002;22(3):380–3.

Abecarnil

General Information

Abecarnil is a partial agonist at the benzodiazepine-GABA receptor complex, and is used in generalized anxiety disorder. Its pharmacology suggests that it may be less likely to produce sedation and tolerance, but data thus far have not shown clear differences in its adverse effects from those of classical benzodiazepines, such as alprazolam, diazepam, and lorazepam. As expected, both acute adverse effects and tolerance are dose-related.

In a multicenter, double-blind trial, abecarnil (mean daily dose 12 mg), diazepam (mean daily dose 22 mg), or placebo were given in divided doses for 6 weeks to 310 patients with generalized anxiety disorder (1). Those who had improved at 6 weeks could volunteer to continue double-blind treatment for a total of 24 weeks. Slightly more patients who took diazepam (77%) and placebo (75%) completed the 6-week study than those who took abecarnil (66%). The major adverse events during abecarnil therapy were similar to those of diazepam, namely drowsiness, dizziness, fatigue, and difficulty in coordination. Abecarnil and diazepam both produced statistically significantly more symptom relief than placebo at 1 week, but at 6 weeks only diazepam was superior to placebo. In contrast to diazepam, abecarnil did not cause withdrawal symptoms. The absence of a placebo control makes it difficult to interpret the results of another study of the use of abecarnil and diazepam in alcohol withdrawal, which appeared to show comparable efficacy and adverse effects of the two drugs (2).

References

1. Rickels K, DeMartinis N, Aufdembrinke B. A double-blind, placebo-controlled trial of abecarnil and diazepam in the treatment of patients with generalized anxiety disorder. J Clin Psychopharmacol 2000;20(1):12–18.
2. Anton RF, Kranzler HR, McEvoy JP, Moak DH, Bianca R. A double-blind comparison of abecarnil and diazepam in the treatment of uncomplicated alcohol withdrawal. Psychopharmacology (Berl) 1997;131(2):123–9.

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In a phase-2, partly randomized, double-blind, placebo-controlled study of three different doses of abetimus in 58 patients, seven did not receive all doses because of adverse events (2). Five withdrew because of adverse events related to their lupus erythematosus: non-renal exacerbations ($n = 2$), hematuria and hypertension ($n = 1$), worsening rash ($n = 1$), and nephritis ($n = 1$). One patient withdrew because of cellulitis and another because of a localized *Herpes zoster* infection. None of the reported adverse events was considered to be definitely related to the drug.

Subsequently, La Jolla Pharmaceuticals terminated two previously established licensing agreements for abetimus (3). One of the agreements was with Leo Pharmaceutical Products of Denmark, which was licensed to market abetimus in Europe and the Middle East, and the other was with Abbott Laboratories. Abbott returned all rights to abetimus to La Jolla Pharmaceuticals in September 1999, based on the results of an analysis of a phase-2/phase-3 trial of abetimus in patients with systemic lupus erythematosus and a history of renal disease, which had been stopped in May 1999 because the primary end-point (the time to worsening of renal function) was much shorter than expected. A further analysis then showed that the number of exacerbations in responders treated with abetimus was less than half the number in the patients treated with placebo. Responders also had a significant reduction in the use of high-dose glucocorticoids and cyclophosphamide.

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In September 2000, the US FDA granted orphan drug status to abetimus for the treatment of lupus nephritis; the EU did likewise in November 2001.

References

1. Coutts SM, Plunkett ML, Iverson GM, Barstad PA, Berner CM. Pharmacological intervention in antibody mediated disease. Lupus 1996;5(2):158–9.
2. Furie RA, Cash JM, Cronin ME, Katz RS, Weisman MH, Aranow C, Liebling MR, Hudson NP, Berner CM, Coutts S,

24. Schell DA, Ganti AK, Levitt R, Potti A. Thrombocytopenia associated with c7E3 Fab (abciximab). Ann Hematol 2002;81(2):76–9.
25. Dery JP, Braden GA, Lincoff AM, Kereiakes DJ, Browne K, Little T, George BS, Sane DC, Cines DB, Effron MB, Mascelli MA, Langrall MA, Damaraju L, Barnathan ES, Tcheng JE; ReoPro Readministration Registry Investigators. Final results of the ReoPro readministration registry. Am J Cardiol 2004;93(8):979–84.
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2. Furie RA, Cash JM, Cronin ME, Katz RS, Weisman MH, Aranow C, Liebling MR, Hudson NP, Berner CM, Coutts S,

de Haan HA. Treatment of systemic lupus erythematosus with LJP 394. J Rheumatol 2001;28(2):257–65.
3. Anonymous. Abetimus: Abetimus sodium, LJP 394. BioDrugs 2003;17(3):212–15.

Acamprosate

General Information

Acamprosate (calcium acetylhomotaurinate) has been postulated to act by restoring the alcohol-induced neurotransmission imbalance of inhibition-excitation inputs believed to underlie alcohol dependence (1,2). The molecular structure of acamprosate explains its specificity toward the basic molecular mechanisms involved in the pathophysiology of alcohol dependence. A competitive interaction has been described between spermidine and acamprosate, suggesting a specific binding site for acamprosate on *N*-methyl-D-aspartate receptors (3).

To test the role of acamprosate as an aid in preventing relapse after detoxification, 296 alcohol-dependent patients entered a prospective, multicenter, randomized, double-blind, placebo-controlled study of acamprosate 666 mg tablets tds for 180 days (4). Unlike previous studies, acamprosate was prescribed from the start of alcohol withdrawal, rather than after the detoxification process. During the treatment period, 110 patients dropped out. The two treatment groups were balanced with regard to baseline values and reasons for discontinuation. There was no difference between the groups in the severity of withdrawal symptoms, as measured by the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol scale). Acamprosate given during withdrawal did not cause unwanted effects. The overall incidence of adverse events was similar in the two groups. The number of patients who presented at least one new adverse event (not present at baseline) during the course of the study was 99 with acamprosate and 94 with placebo. Nevertheless, there was a trend for gastrointestinal adverse events to be reported more often in the acamprosate-treated patients ($n = 61$) compared with placebo ($n = 46$). The individual adverse events that were reported more often with acamprosate were diarrhea, dyspepsia, constipation, and flatulence. Pruritus was reported by seven of those who took acamprosate and five of those who took placebo.

Organs and Systems

Gastrointestinal

Acamprosate can cause diarrhea and mild abdominal pain (5).

References

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Acebutolol

See also Beta-adrenoceptor antagonists

General Information

Acebutolol is a beta-adrenoceptor antagonist with membrane-stabilizing activity that is sometimes cited as being cardioselective but has considerable effects on bronchioles and peripheral blood vessels.

Organs and Systems

Respiratory

Bronchiolitis obliterans has been attributed to acebutolol (1).

Liver

Six cases of reversible hepatitis have been attributed to acebutolol (2).

Immunologic

Patients taking acebutolol relatively commonly develop antinuclear antibodies (3,4).

Drug Administration

Drug overdose

The membrane-stabilizing activity of beta-blockers can play a major role in toxicity. Of 208 deaths in subjects who had taken beta-blockers, 206 occurred with drugs that have membrane-stabilizing activity. This quinidine-like effect can be reversed by sodium bicarbonate, which is also used to counteract the cardiotoxic effects of cyclic antidepressants, which also have membrane-stabilizing activity.

- An overdose of acebutolol (6.4 mg) in a 48-year-old man caused cardiac arrest with ventricular tachycardia (5). An intravenous bolus of sodium bicarbonate 50 mmol produced sinus rhythm.

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de Haan HA. Treatment of systemic lupus erythematosus with LJP 394. J Rheumatol 2001;28(2):257–65.
3. Anonymous. Abetimus: Abetimus sodium, LJP 394. BioDrugs 2003;17(3):212–15.

Acamprosate

General Information

Acamprosate (calcium acetylhomotaurinate) has been postulated to act by restoring the alcohol-induced neurotransmission imbalance of inhibition-excitation inputs believed to underlie alcohol dependence (1,2). The molecular structure of acamprosate explains its specificity toward the basic molecular mechanisms involved in the pathophysiology of alcohol dependence. A competitive interaction has been described between spermidine and acamprosate, suggesting a specific binding site for acamprosate on *N*-methyl-D-aspartate receptors (3).

To test the role of acamprosate as an aid in preventing relapse after detoxification, 296 alcohol-dependent patients entered a prospective, multicenter, randomized, double-blind, placebo-controlled study of acamprosate 666 mg tablets tds for 180 days (4). Unlike previous studies, acamprosate was prescribed from the start of alcohol withdrawal, rather than after the detoxification process. During the treatment period, 110 patients dropped out. The two treatment groups were balanced with regard to baseline values and reasons for discontinuation. There was no difference between the groups in the severity of withdrawal symptoms, as measured by the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol scale). Acamprosate given during withdrawal did not cause unwanted effects. The overall incidence of adverse events was similar in the two groups. The number of patients who presented at least one new adverse event (not present at baseline) during the course of the study was 99 with acamprosate and 94 with placebo. Nevertheless, there was a trend for gastrointestinal adverse events to be reported more often in the acamprosate-treated patients ($n = 61$) compared with placebo ($n = 46$). The individual adverse events that were reported more often with acamprosate were diarrhea, dyspepsia, constipation, and flatulence. Pruritus was reported by seven of those who took acamprosate and five of those who took placebo.

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Acecainide

See also Antidysrhythmic drugs

General Information

Acecainide (*N*-acetylprocainamide) is the main metabolite of procainamide, and it has antidysrhythmic activity (1). However, in contrast to procainamide, which has Class Ib activity, the main action of acecainide is that of Class III.

Apart from the lupus-like syndrome, the adverse effects of acecainide are as common as those of procainamide. The commonest affect the gastrointestinal tract and the central nervous system. Anorexia, nausea, vomiting, diarrhea, and abdominal pain are common, as are insomnia, dizziness, light-headedness, tingling sensations, and blurred vision. Other reported unwanted effects include skin rashes, constipation, and reduced sexual function (2–5).

Organs and Systems

Cardiovascular

Acecainide prolongs the QT interval and can therefore cause ventricular dysrhythmias (6). The risk is increased in renal insufficiency, since acecainide is mainly eliminated unchanged via the kidneys.

Immunologic

The main advantage of acecainide over procainamide is the lower incidence of the lupus-like syndrome. Many fewer patients develop antinuclear antibodies during long-term treatment with acecainide than during long-term treatment with procainamide (7).

There are also reports of remission of lupus-like syndrome without recurrence in patients in whom acecainide has been used as a replacement for procainamide (8–10). Furthermore, patients in whom procainamide has previously caused a lupus-like syndrome have been reported not to suffer from the syndrome on subsequent long-term treatment with acecainide (8). However, one patient suffered mild arthralgia while taking acecainide, having had a more severe arthropathy while taking procainamide (8).

Susceptibility Factors

Renal disease

Because acecainide is eliminated mostly unchanged by renal excretion, with a half-life of about 7 hours, its clearance is reduced in patients with renal impairment, who are at increased risk of adverse effects. This means that elderly people, who generally have a degree of renal impairment, are also at increased risk.

Monitoring Drug Therapy

The target plasma concentration range of acecainide is 15–25 μg/ml. The adverse effects of acecainide increase in frequency at concentrations above 30 μg/ml (11).

References

1. Atkinson AJ Jr, Ruo TI, Piergies AA. Comparison of the pharmacokinetic and pharmacodynamic properties of procainamide and N-acetylprocainamide. Angiology 1988;39(7 Pt 2):655–67.
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3. Winkle RA, Jaillon P, Kates RE, Peters F. Clinical pharmacology and antiarrhythmic efficacy of N-acetylprocainamide. Am J Cardiol 1981;47(1):123–30.
4. Atkinson AJ Jr, Lertora JJ, Kushner W, Chao GC, Nevin MJ. Efficacy and safety of N-acetylprocainamide in long-term treatment of ventricular arrhythmias. Clin Pharmacol Ther 1983;33(5):565–76.
5. Domoto DT, Brown WW, Bruggensmith P. Removal of toxic levels of N-acetylprocainamide with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration. Ann Intern Med 1987;106(4):550–2.
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7. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide. N Engl J Med 1979;301(25):1382–5.
8. Kluger J, Leech S, Reidenberg MM, Lloyd V, Drayer DE. Long-term antiarrhythmic therapy with acetylprocainamide. Am J Cardiol 1981;48(6):1124–32.
9. Kluger J, Drayer DE, Reidenberg MM, Lahita R. Acetylprocainamide therapy in patients with previous procainamide-induced lupus syndrome. Ann Intern Med 1981;95(1):18–23.
10. Stec GP, Lertora JJ, Atkinson AJ Jr, Nevin MJ, Kushner W, Jones C, Schmid FR, Askenazi J. Remission of procainamide-induced lupus erythematosus with N-acetylprocainamide therapy. Ann Intern Med 1979;90(5):799–801.
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Aceclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

Despite claims that aceclofenac is a COX-2 selective inhibitor, experience shows that its adverse effects profile is similar to that of the non-selective NSAIDs.

Organs and Systems

Gastrointestinal

Symptoms of gastrointestinal intolerance in patients taking aceclofenac commonly require withdrawal, at a rate of 3–15% (SEDA-20, 91).

Liver

Acute hepatitis has been reported with aceclofenac (SEDA-21, 103).

Skin

Aceclofenac cream can cause erythema, itching, and a burning sensation in under 3% of patients (SEDA-20, 91).

Aceclofenac can cause photosensitivity.

- After starting twice-daily topical application of a cream containing aceclofenac, a woman developed acute eczema affecting the sun-exposed areas of her legs (1).

Immunologic

A hypersensitivity reaction characterized by multiple purpuric lesions and reduced renal function has been described in an elderly patient (SEDA-18, 103), and there have been reports of hypersensitivity vasculitis (SEDA-20, 91) (SEDA-21, 103).

Reference

1. Goday Bujan JJ, Garcia Alvarez-Eire GM, Martinez W, del Pozo J, Fonseca E. Photoallergic contact dermatitis from aceclofenac. Contact Dermatitis 2001;45(3):170.

Acemetacin

See also Non-steroidal anti-inflammatory drugs

General Information

Acemetacin is an indometacin derivative with the same adverse effects profile (SEDA-6, 94). In an open multicenter study, 187 of 280 patients had adverse effects (57% gastrointestinal); treatment had to be stopped in 7% (1). The use of acemetacin is limited and there is no justification for claims that it has advantages over existing NSAIDs.

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Acetylcholinesterase inhibitors

General Information

Cholinesterase inhibitors increase parasympathetic nervous system (cholinergic) activity indirectly by inhibiting acetylcholinesterase, thereby preventing the breakdown of acetylcholine. They are only effective in the presence of acetylcholine. They are listed in Table 1.

The cholinesterase inhibitors are used in the treatment of Alzheimer's disease (tacrine, 7-methoxytacrine, donepezil, metrifonate, and rivastigmine), the treatment and diagnosis of myasthenia gravis (distigmine, edrophonium, neostigmine, physostigmine, prostigmine, and pyridostigmine), and the treatment of atony of the intestine or bladder. In the eye, they increase the flow rate of aqueous humor across the trabeculum, reduce resistance to its flow, and consequently lower the intraocular pressure.

Use of acetylcholinesterase inhibitors in Alzheimer's disease

Of the acetylcholinesterase inhibitors, tacrine, methoxytacrine, metrifonate, donepezil hydrochloride, and rivastigmine are used in the treatment of Alzheimer's disease. In 12–30% of patients with Alzheimer's disease, tacrine causes an increase in hepatic transaminase activity. Abdominal adverse effects are very frequent, for example nausea, anorexia, diarrhea. The peripheral cholinomimetic effects of tacrine occur in a very high proportion of patients, probably the majority. The hepatic effects seem to be such that the use of these new (and in some cases still experimental) drugs would not be justified in

Table 1 Acetylcholinesterase inhibitors

Ambenonium
Diisopropyl fluorophosphate (Diflos)
Distigmine
Donepezil
Ecothiopate
Edrophonium
Eserine
Methoxytacrine
Metrifonate
Neostigmine
Physostigmine
Prostigmine
Pyridostigmine
Rivastigmine
Tacrine and 7-methoxytacrine

Aceclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

Despite claims that aceclofenac is a COX-2 selective inhibitor, experience shows that its adverse effects profile is similar to that of the non-selective NSAIDs.

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Aceclofenac cream can cause erythema, itching, and a burning sensation in under 3% of patients (SEDA-20, 91).

Aceclofenac can cause photosensitivity.

- After starting twice-daily topical application of a cream containing aceclofenac, a woman developed acute eczema affecting the sun-exposed areas of her legs (1).

Immunologic

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Reference

1. Heiter A, Tausch G, Eberl R. Ergebnisse einer Langstudie mit Acemetacin bei der Behandlung von Patienten mit chronischer Polyarthritis. [Results of a long-term study with acemetacin in the therapy of patients suffering from rheumatoid arthritis.] Arzneimittelforschung 1980;30(8A):460–3.

Acetylcholinesterase inhibitors

General Information

Cholinesterase inhibitors increase parasympathetic nervous system (cholinergic) activity indirectly by inhibiting acetylcholinesterase, thereby preventing the breakdown of acetylcholine. They are only effective in the presence of acetylcholine. They are listed in Table 1.

The cholinesterase inhibitors are used in the treatment of Alzheimer's disease (tacrine, 7-methoxytacrine, donepezil, metrifonate, and rivastigmine), the treatment and diagnosis of myasthenia gravis (distigmine, edrophonium, neostigmine, physostigmine, prostigmine, and pyridostigmine), and the treatment of atony of the intestine or bladder. In the eye, they increase the flow rate of aqueous humor across the trabeculum, reduce resistance to its flow, and consequently lower the intraocular pressure.

Use of acetylcholinesterase inhibitors in Alzheimer's disease

Of the acetylcholinesterase inhibitors, tacrine, methoxytacrine, metrifonate, donepezil hydrochloride, and rivastigmine are used in the treatment of Alzheimer's disease. In 12–30% of patients with Alzheimer's disease, tacrine causes an increase in hepatic transaminase activity. Abdominal adverse effects are very frequent, for example nausea, anorexia, diarrhea. The peripheral cholinomimetic effects of tacrine occur in a very high proportion of patients, probably the majority. The hepatic effects seem to be such that the use of these new (and in some cases still experimental) drugs would not be justified in

Table 1 Acetylcholinesterase inhibitors

Ambenonium
Diisopropyl fluorophosphate (Diflos)
Distigmine
Donepezil
Ecothiopate
Edrophonium
Eserine
Methoxytacrine
Metrifonate
Neostigmine
Physostigmine
Prostigmine
Pyridostigmine
Rivastigmine
Tacrine and 7-methoxytacrine

other-than-serious disease states, but they are reversible if the drug is withdrawn.

General adverse effects

The acetylcholinesterase inhibitors have the effects that one would expect to result from their promoting nicotinic and muscarinic cholinergic activity, including unwanted effects such as bradycardia, miosis, colic, and hypersalivation. Adverse reactions have been stated to be relatively more common with neostigmine than with some other drugs such as pyridostigmine or ambenonium, but it is doubtful whether the benefit to harm balance indeed differs, since neostigmine also tends to be more effective in certain patients. Ambenonium is relatively likely to cause headache. When neostigmine and pyridostigmine are used as bromide salts, bromide rashes can occur.

Local adverse effects

Acetylcholinesterase inhibitors as eye drops have more intense effects in myopic and young patients, causing aggravation of myopia, blurred vision, and periorbital pain, due to congestion of the iris and ciliary body. Anterior and posterior synechiae can develop. Allergic reactions have been reported as has epithelial toxicity. The acetylcholinesterase inhibitors can cause pseudopemphigoid reactions in the eyelids and occlusion of the lacrimal puncta (SED-12, 1198) (1). The danger that a miotic agent will produce retinal detachment is directly proportional to the capacity of the drug to produce spasm of the ciliary body. Retinal detachment has been reported after the use of cholinergic agents, but they can also be coincidental.

Systemic effects

The commonest effects of the acetylcholinesterase inhibitors are headache and periorbital pain. Signs of vagal stimulation can occur, with nausea, vomiting, sweating, hypersalivation, lacrimation, hypotension, bradycardia, bronchial constriction, respiratory failure, and nightmares. These reactions essentially occur during intensive treatment for acute closed-angle glaucoma, requiring frequent instillations of pilocarpine. Elderly people and young children are at particular risk.

Organs and Systems

Cardiovascular

With any acetylcholinesterase inhibitor, bradycardia can, with excessive dosage, proceed to dysrhythmias (SEDA-13, 114) and even asystole.

- A 67-year-old man underwent left upper lobectomy for a presumed malignancy 11 years after cardiac transplantation (2). He had had no cardiac symptoms since his transplant. Suxamethonium was used as a muscle relaxant and was reversed with glycopyrrolate 0.8 mg and neostigmine 4 mg. Within a few minutes, he developed asystole, which lasted for about 45 seconds. He subsequently made a full recovery.

The authors speculated that some degree of cardiac reinnervation may have occurred; they recommended that this type of response should be anticipated in future anesthesia in such patients and that therapeutic measures, such as a beta-adrenoceptor agonist, should be available.

Another case of asystole has been reported with the very short-acting cholinesterase inhibitor edrophonium (3).

- A 49-year-old woman was given intravenous edrophonium chloride 2 mg as part of the investigation of an acute myopathy following gastrointestinal surgery. She had also received 60 mg of intravenous labetalol in the 14 hours before the edrophonium was given: presumably this was for a raised blood pressure, but that was not specified. Labetalol caused transient but severe bradycardia (heart rate about 20/minute). Immediately after the injection of edrophonium, she developed asystole, which was treated immediately with atropine and recovered in 10 seconds.

Such reactions are extremely rare, but in this case the risk was undoubtedly enhanced by previous beta-blockade.

With physostigmine, hypertension has been both demonstrated in animal experiments and observed in a series of patients after intravenous use in relatively high doses; it has also occurred during use of low doses of oral physostigmine in an elderly patient with Alzheimer's disease (SEDA-12, 125).

Nervous system

During a trial of oral physostigmine, myoclonus occurred in two patients with probable Alzheimer's disease (SEDA-12, 125).

Gastrointestinal

To reduce the incidence of residual paralysis after the administration of non-depolarizing neuromuscular blocking agents, some advocate the routine use of anticholinesterase drugs at the end of surgery. However, it has been suggested that this practice might increase the risk of postoperative nausea and vomiting. Clinical trials have produced contradictory results. A meta-analysis of the available data suggested that omitting routine neostigmine may reduce the incidence of emesis only when a large dose (2.5 mg) is used (4). With a smaller dose (1.5 mg), there was no difference. The incidence of clinically relevant residual paralysis was 1 in 30 in the control groups. There were no cases of residual curarization in the treatment groups when either edrophonium 500 μg/kg or neostigmine 1.5 mg was given in combination with atropine. Therefore, the question of whether or not routine anticholinesterase administration is beneficial for the patient is still open to debate. Other adverse effects of anticholinesterase drugs, such as bronchial hypersecretion or intestinal hypermotility, could increase morbidity, and we do not know whether all of these adverse effects are completely blocked by the concomitant use of a parasympatholytic agent (5). It should be taken into account that the incidence of residual curarization may be reduced as effectively by the use of neuromuscular transmission monitoring (6,7). Some believe that anticholinesterase drugs should be used to reverse residual neuromuscular block that produces clinical symptoms or is detected by neuromuscular transmission monitoring.

Musculoskeletal

Any acetylcholinesterase inhibitor can produce muscular fasciculation followed by voluntary muscle paralysis, and these muscular effects can serve as a valuable sign of approaching overdosage. Two patients, one with dystrophia myotonica and the other with progressive muscular dystrophy, presented with respiratory difficulties, necessitating prolonged mechanical ventilation. As these difficulties are as good as impossible to predict, short-acting neuromuscular blockers should preferably be used, thus avoiding the need for pharmacological reversal (8).

Immunologic

Severe urticaria and anaphylaxis associated with pyridostigmine (an unspecified dose) occurred in a 54-year-old woman with myasthenia gravis (9). Urticaria started almost immediately after introduction of the drug but was partially controlled by the antihistamine cetirizine. However, pyridostigmine was stopped after 2 months and the urticaria resolved completely. Rechallenge with oral pyridostigmine led to an anaphylactic reaction that was treated with subcutaneous adrenaline. There were no sequelae.

Second-Generation Effects

Teratogenicity

Microcephaly occurred in the child of a woman taking a high dose of pyridostigmine (10).

- A 24-year-old woman had suffered from myasthenia gravis from the unusually early age of 10 years. During her first pregnancy, pyridostigmine was her sole medication. Because of deterioration in her symptoms during the pregnancy, the dosage was increased until she was taking 1500–3000 mg/day, or 4–8 times the maximum recommended dose. This still did not produce much clinical improvement but was nevertheless continued throughout the pregnancy. She needed an emergency cesarean section at 36 weeks because of fetal bradycardia. The baby was microcephalic.

The authors failed to find any other cause for this abnormality and concluded that the excessive dose of pyridostigmine had been responsible for the fetal damage.

Fetotoxicity

Acetylcholinesterase inhibitors can probably be safely used in pregnancy when needed, provided the dosage is carefully regulated. Reversible muscle weakness in a newborn infant was attributed to relative overdosage of the mother with pyridostigmine bromide (11).

Susceptibility Factors

Age

Elderly people need to be treated with caution because of their greater susceptibility to the cardiovascular effects of the acetylcholinesterase inhibitors; this is particularly relevant to their use in Alzheimer's disease.

Other features of the patient

Special caution is recommended when acetylcholinesterase inhibitors are given to patients with inflammatory, infiltrative, or degenerative disease of the cardiac conducting system, patients taking digitalis, calcium channel blockers, or beta-blockers, and patients with myocardial ischemia. Appropriate resuscitative equipment should be readily available.

Neostigmine or other anticholinesterase inhibitors are regularly used in anesthesia to reverse neuromuscular block; however, in patients with neuromuscular disorders, this reversal can present unforeseen difficulties. All anticholinesterase inhibitors must be cautiously dosed if severe adverse reactions are to be avoided. When these drugs are given orally, administration should be suspended during periods of severe constipation, in light of one reported case in which neostigmine accumulated in the gastrointestinal tract of a child during a constipative phase and was thereafter rapidly absorbed, with fatal results (SED-12, 326). Anticholinesterase drugs are contraindicated in bronchial asthma.

Drug–Drug Interactions

Anticholinergic drugs

The effect of acetylcholinesterase inhibitors can be reduced by drugs with anticholinergic effects, such as antihistamines or neuroleptic drugs (12).

Suxamethonium

Acetylcholinesterase inhibitor eye drops or exposure to organophosphate insecticides can reduce the activity of plasma cholinesterase and pseudocholinesterase, creating a potentially fatal hazard for surgical patients receiving suxamethonium. During induction of general anesthesia, the presence of anticholinesterase activity in the serum can potentiate the effect of curare-like drugs, such as suxamethonium, used as muscle relaxants, with prolonged apnea after intubation and death. Such eye drops should be stopped 6 weeks before the operation. The importance of inquiring about the use of drugs cannot be overemphasized. Patients often do not regard eye drops as medications and omit this information from their medical history. Complaints of excessive sweating, intermittent diarrhea, muscle weakness, and fatigue over a long period may be due to the usage of ecothiopate eye drops (phospholine iodide 0.25%) for glaucoma and can disappear when the eye drops are withdrawn (13).

References

1. Friart A, Hermans L, De Valeriola Y. Unusual side-effect of a dobutamine stress echocardiography. Am J Noninvasive Cardiol 1993;7:63–4.
2. Bjerke RJ, Mangione MP. Asystole after intravenous neostigmine in a heart transplant recipient. Can J Anaesth 2001;48(3):305–7.
3. Okun MS, Charriez CM, Bhatti MT, Watson RT, Swift TR. Asystole induced by edrophonium following beta blockade. Neurology 2001;57(4):739.

4. Tramèr MR, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. Br J Anaesth 1999;82(3):379–86.
5. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. Anesthesiology 1992;77(4):785–805.
6. Mortensen R, Berg H, El-Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. Acta Anaesthesiol Scand 1995;39(6):797–801.
7. Shorten GD, Merk H, Sieber T. Perioperative train-of-four monitoring and residual curarization. Can J Anaesth 1995;42(8):711–15.
8. Buzello W, Krieg N, Schlickewei A. Hazards of neostigmine in patients with neuromuscular disorders. Report of two cases. Br J Anaesth 1982;54(5):529–34.
9. Castellano A, Cabrera M, Robledo T, Martinez-Cocera C, Cimarra M, Llamazares AA, Chamorro M. Anaphylaxis by pyridostigmine. Allergy 1998;53(11):1108–9.
10. Niesen CE, Shah NS. Pyridostigmine-induced microcephaly. Neurology 2000;54(9):1873–4.
11. Blackhall MI, Buckley GA, Roberts DV, Roberts JB, Thomas BH, Wilson A. Drug-induced neonatal myasthenia. J Obstet Gynaecol Br Commonw 1969;76(2):157–62.
12. Carnahan RM, Lund BC, Perry PJ, Chrischilles EA. The concurrent use of anticholinergics and cholinesterase inhibitors: rare event or common practice? J Am Geriatr Soc 2004;52(12):2082–7.
13. Alexander WD. Systemic side effects with eye drops. BMJ (Clin Res Ed) 1981;282(6273):1359.

Acetylcysteine

General Information

Acetylcysteine (*N*-acetylcysteine) is used as a mucolytic and to treat paracetamol overdose.

Acetylcysteine splits disulfide bonds in mucoproteins and thus lowers mucus viscosity, resulting in a larger volume of sputum. It is normally administered by inhalation as a nebulized solution or aerosol, although it can also be taken orally. Acetylcysteine is also an antioxidant and may protect the lung from free radicals generated by inflammatory cells activated by influenza virus infection. Treatment for 6 months with acetylcysteine 600 mg bd significantly reduced the frequency and severity of influenza-like episodes. Adverse effects were reported by 9% of patients who complained of dysuria, epigastric pain, nausea and vomiting, constipation or diarrhea, and flushing (SEDA-22, 195).

The place of mucolytic drugs in respiratory disease has recently been reviewed (1). The authors suggested that they have been inappropriately used in the past. As mucolytic agents do not improve lung function tests in COPD, the European Respiratory Society and the American Thoracic Society guidelines discourage their use in the treatment of COPD. Future trials should evaluate clinical symptoms and quality of life as well as lung function tests. Mucolytic agents should be evaluated earlier in the natural history of COPD, when mucus hypersecretion is the major feature and before lung function has deteriorated.

Acetylcysteine is used intravenously as an antidote for severe paracetamol poisoning, in which it acts as a thiol donor.

Oral acetylcysteine has been investigated for the treatment of cancer. Acetylcysteine 600 mg/day was compared with retinol 300 000 U/day, the combination, and a placebo in a total of 2191 patients treated for 2 years. Adverse effects were reported by 14% of those who took acetylcysteine, compared with 23% of those who took retinol and 25% of those who took the combination. The most common adverse effect attributed to acetylcysteine was dyspepsia. In healthy volunteers, higher doses of acetylcysteine, 600 mg taken two or three times daily for 4 weeks, caused more adverse effects: 25 and 61% of the volunteers, respectively, reported gastrointestinal adverse effects (SEDA-20, 184).

There has been a systematic review of published randomized studies of the use of *N*-acetylcysteine in chronic bronchitis (2). A total of 39 trials were considered, of which only nine were included in the meta-analysis. In all cases, oral *N*-acetylcysteine had been used in a dosage of 200–300 mg bd for 4–32 weeks. There were gastrointestinal adverse effects (dyspepsia, diarrhea, and heartburn) in 10% of 2011 patients, and 6.5% withdrew because of their symptoms. However, the rate of gastrointestinal adverse effects was higher in the placebo group (11% with a withdrawal rate of 7.1%). There was no exacerbation of chronic bronchitis in 49% of patients treated with acetylcysteine compared with 31% of placebo-treated patients, a relative benefit of 1.56 (95% CI = 1.37, 1.77). There was also symptom improvement with treatment: 61% reported improvement in symptoms with acetylcysteine compared with 35% with placebo.

Organs and Systems

Respiratory

Aerosol therapy with acetylcysteine can cause bronchoconstriction. In 31 ambulant asthmatics using 10% acetylcysteine solution, there was a mean reduction of 55% in the FEV_1 in 19 subjects. The addition of 0.05% isoprenaline reduced the number of patients who developed bronchoconstriction from 19 to 5 (SEDA-5, 170). In two placebo-controlled studies, involving over 700 patients, there was no difference in adverse effects between oral acetylcysteine and a placebo. There was, however, no improvement in FEV_1 in these studies (3).

Immunologic

Hypersensitivity reactions have been reported when acetylcysteine is given intravenously in paracetamol overdose. A generalized erythematous rash can develop, and itching, nausea, vomiting, dizziness, and severe breathlessness with bronchospasm and tachycardia have been reported (SEDA-5, 170). Angioedema with hypotension and bronchospasm have also been described (4). Wheal responses to high concentrations of acetylcysteine (20 mg/ml) were significantly greater in those who reacted to the drug. In two patients with a positive reaction the response could be inhibited by prior therapy with an antihistamine. As hypersensitivity reactions have been reported in up to

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3% of patients receiving intravenous acetylcysteine for paracetamol overdose, physicians need to be prepared for these reactions (5). A pseudo-allergic reaction on the basis of histamine liberation, rather than an immunological etiology, is suggested as the mechanism (6,7).

Management guidelines for the treatment of anaphylactoid reactions to intravenous acetylcysteine have been developed. Patients who develop only flushing of the skin require no treatment. Urticaria should be treated with diphenhydramine and acetylcysteine infusion can be continued. If angioedema or respiratory distress occur, diphenhydramine should be given and the acetylcysteine infusion stopped; it can be restarted 1 hour after the administration of diphenhydramine if no symptoms are present (SEDA-22, 195).

Drug–Drug Interactions

Antibiotics

The 5% solution, for inhalation, almost completely inactivates penicillin and cephalosporins in vitro and reduces the activity of tetracycline.

References

1. Del Donno M, Olivieri D. Mucoactive drugs in the management of chronic obstructive pulmonary disease. Monaldi Arch Chest Dis 1998;53(6):714–19.
2. Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. Eur Respir J 2000;16(2):253–62.
3. British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. Thorax 1985;40(11):832–5.
4. Mant TG, Tempowski JH, Volans GN, Talbot JC. Adverse reactions to acetylcysteine and effects of overdose. BMJ (Clin Res Ed) 1984;289(6439):217–19.
5. Bonfiglio MF, Traeger SM, Hulisz DT, Martin BR. Anaphylactoid reaction to intravenous acetylcysteine associated with electrocardiographic abnormalities. Ann Pharmacother 1992;26(1):22–5.
6. Bateman DN, Woodhouse KW, Rawlins MD. Adverse reactions to N-acetylcysteine. Lancet 1984;2(8396):228.
7. Tenenbein M. Hypersensitivity-like reactions to N-acetylcysteine. Vet Hum Toxicol 1984;26(Suppl 2):3–5.

Acetylsalicylic acid

General Information

A century after its introduction, acetylsalicylic acid (aspirin) is by far the most commonly used analgesic, sharing its leading position with the relative newcomer paracetamol (acetaminophen), and notwithstanding the fact that other widely used compounds of their class, like ibuprofen and naproxen, have in recent years been introduced in over-the-counter versions. Both are also still being prescribed by physicians and are generally used for mild to moderate pain, fever associated with common everyday illnesses, and disorders ranging from head colds and influenza to toothache and headache. Their greatest use is by consumers who obtain them directly at the pharmacy, and in many countries outside pharmacies as well. Perhaps this wide availability and advertising via mass media lead to a lack of appreciation by the lay public that these are medicines with associated adverse effects. Both have at any rate been subject to misuse and excessive use, leading to such problems as chronic salicylate intoxication with aspirin, and severe hepatic damage after overdose with paracetamol. Both aspirin and paracetamol have featured in accidental overdosage (particularly in children) as well as intentional overdosage.

In an investigation of Canadian donors who had not admitted to drug intake, 6–7% of the blood samples taken were found to have detectable concentrations of acetylsalicylic acid and paracetamol (1). Such drugs would be potentially capable of causing untoward reactions in the recipients.

To offer some protection against misuse of analgesics, many countries have insisted on the use of packs containing total quantities less than the minimum toxic dose (albeit usually the one obtained for healthy young volunteers and thus disregarding the majority of the population), and supplied in child-resistant packaging. Most important, however, is the need to provide education for the lay public to respect such medicines in general for the good they can do, but more especially for the harm that can arise but which can be avoided. There is a definite role for the prescribing physician, as informing the patient seems to prevent adverse events (2).

The sale of paracetamol or aspirin in dosage forms in which they are combined with other active ingredients offers considerable risk to the consumer, since the product as sold may not be clearly identified as containing either of these two analgesics. Brand names sometimes obscure the actual composition of older formulations that contain one or both of these analgesics in combination with, for example, a pyrazolone derivative and/or a potentially addictive substance. For instance, in Germany, with the EC harmonization of the Drug Law of 1990, the manufacturers of drugs already marketed before 1978 had the opportunity of exchanging even the active principles without being obliged to undergo a new approval procedure or to abandon their brand name. Combination formulations are still being promoted and sold, and not exclusively in developing countries. Consequently, the patient who is so anxious to allay all his symptoms that he takes several medications concurrently may without knowing it take several doses of aspirin or paracetamol at the same time, perhaps sufficient to cause toxicity. It is essential that product labels clearly state their active ingredients by approved name together with the quantity per dosage form (3).

The antipyretic analgesics, with the non-steroidal anti-inflammatory drugs (NSAIDs), share a common mechanism of action, namely the inhibition of prostaglandin synthesis from arachidonic acid and their release. More precisely their mode of action is thought to result from inhibition of both the constitutive and the

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A century after its introduction, acetylsalicylic acid (aspirin) is by far the most commonly used analgesic, sharing its leading position with the relative newcomer paracetamol (acetaminophen), and notwithstanding the fact that other widely used compounds of their class, like ibuprofen and naproxen, have in recent years been introduced in over-the-counter versions. Both are also still being prescribed by physicians and are generally used for mild to moderate pain, fever associated with common everyday illnesses, and disorders ranging from head colds and influenza to toothache and headache. Their greatest use is by consumers who obtain them directly at the pharmacy, and in many countries outside pharmacies as well. Perhaps this wide availability and advertising via mass media lead to a lack of appreciation by the lay public that these are medicines with associated adverse effects. Both have at any rate been subject to misuse and excessive use, leading to such problems as chronic salicylate intoxication with aspirin, and severe hepatic damage after overdose with paracetamol. Both aspirin and paracetamol have featured in accidental overdosage (particularly in children) as well as intentional overdosage.

In an investigation of Canadian donors who had not admitted to drug intake, 6–7% of the blood samples taken were found to have detectable concentrations of acetylsalicylic acid and paracetamol (1). Such drugs would be potentially capable of causing untoward reactions in the recipients.

To offer some protection against misuse of analgesics, many countries have insisted on the use of packs containing total quantities less than the minimum toxic dose (albeit usually the one obtained for healthy young volunteers and thus disregarding the majority of the population), and supplied in child-resistant packaging. Most important, however, is the need to provide education for the lay public to respect such medicines in general for the good they can do, but more especially for the harm that can arise but which can be avoided. There is a definite role for the prescribing physician, as informing the patient seems to prevent adverse events (2).

The sale of paracetamol or aspirin in dosage forms in which they are combined with other active ingredients offers considerable risk to the consumer, since the product as sold may not be clearly identified as containing either of these two analgesics. Brand names sometimes obscure the actual composition of older formulations that contain one or both of these analgesics in combination with, for example, a pyrazolone derivative and/or a potentially addictive substance. For instance, in Germany, with the EC harmonization of the Drug Law of 1990, the manufacturers of drugs already marketed before 1978 had the opportunity of exchanging even the active principles without being obliged to undergo a new approval procedure or to abandon their brand name. Combination formulations are still being promoted and sold, and not exclusively in developing countries. Consequently, the patient who is so anxious to allay all his symptoms that he takes several medications concurrently may without knowing it take several doses of aspirin or paracetamol at the same time, perhaps sufficient to cause toxicity. It is essential that product labels clearly state their active ingredients by approved name together with the quantity per dosage form (3).

The antipyretic analgesics, with the non-steroidal anti-inflammatory drugs (NSAIDs), share a common mechanism of action, namely the inhibition of prostaglandin synthesis from arachidonic acid and their release. More precisely their mode of action is thought to result from inhibition of both the constitutive and the

inducible isoenzymes (COX-1 and COX-2) of the cyclooxygenase pathway (4). However, aspirin and paracetamol are distinguishable from most of the NSAIDs by their ability to inhibit prostaglandin synthesis in the nervous system, and thus the hypothalamic center for body temperature regulation, rather than acting mainly in the periphery.

Endogenous pyrogens (and exogenous pyrogens that have their effects through the endogenous group) induce the hypothalamic vascular endothelium to produce prostaglandins, which activate the thermoregulatory neurons by increasing AMP concentrations. The capacity of the antipyretic analgesics to inhibit hypothalamic prostaglandin synthesis appears to be the basis of their antipyretic action. Neither aspirin nor paracetamol affects the synthesis or release of endogenous pyrogens and neither will lower body temperature if it is normal.

While aspirin significantly inhibits peripheral prostaglandin and thromboxane synthesis, paracetamol is less potent as a synthetase inhibitor than the NSAIDs, except in the brain, and paracetamol has only a weak anti-inflammatory action. It is simple to ascribe the analgesic activity of aspirin to its capacity to inhibit prostaglandin synthesis, with a consequent reduction in inflammatory edema and vasodilatation, since aspirin is most effective in the pain associated with inflammation or injury. However, such a peripheral effect cannot account for the analgesic activity of paracetamol, which is less well understood.

As a prostaglandin synthesis inhibitor, aspirin, like other NSAIDs, is associated with irritation of and damage to the gastrointestinal mucosa. In low doses it can also increase bleeding by inhibiting platelet aggregation; in high doses, prolongation of the prothrombin time will contribute to the bleeding tendency. Intensive treatment can also produce unwanted nervous system effects (salicylism).

Depending on the criteria used, the incidence of aspirin hypersensitivity is variously estimated as being as low as 1% or as high as 50%, the highest frequency being found in asthmatics. The condition is characterized by bronchospasm (asthma), urticaria, angioedema, and vasomotor rhinitis, each occurring alone or in combination, often leading to severe and even life-threatening reactions. There is no clear evidence of an association with tumors, apart from the possible peripheral contribution of aspirin to the development of urinary tract neoplasms in patients with analgesic nephropathy. Indeed, some authors have suggested a role for salicylates in reducing the incidence of colorectal tumors and breast tumors.

The following are absolute contraindications to the use of aspirin:

- children under 16;
- people with hypersensitivity to salicylates, NSAIDs, or tartrazine;
- people with peptic ulceration;
- people with known coagulopathies, including those induced as part of medical therapy.

The following are relative contraindications to the use of long-term analgesic doses of aspirin:

- gout, since normal analgesic doses impede the excretion of uric acid (high doses have a uricosuric effect); an additional problem in gout is that salicylates reduce the uricosuric effects of sulfinpyrazone and probenecid;
- variant angina; a daily dose of 4 g has been found to provoke attacks both at night-time and during the day (5,6), perhaps owing to direct triggering of coronary arterial spasm; blockade of the synthesis of PGI_z, which normally protects against vasoconstriction, could be involved;
- diabetes mellitus, in which aspirin can in theory interfere with the actions of insulin and glucagon sufficiently to derange control;
- some days before elective surgery (even in coronary artery bypass grafting) or delivery, especially if extradural anesthesia is used (7), although recent data seem reassuring (8); aspirin increases bleeding at dental extraction or perioperatively;
- in elderly people, who may develop gastrointestinal bleeding;
- anorectal inflammation (suppositories);
- pre-existing gastrointestinal disease, liver disease, hypoalbuminemia, hypovolemia, in the third trimester of pregnancy, perioperatively, or in patients with threatening abortion.

Assessing the benefit-to-harm balance of low-dose aspirin in preventing strokes and heart attacks

Although there is clear evidence of benefit of acetylsalicylic acid (aspirin) in secondary prevention of strokes and heart attacks, the question of whether aspirin should also be prescribed for primary prevention in asymptomatic people is still debatable. Trials in primary prevention have given contrasting results (9,10), and aspirin can cause major harms (for example severe gastrointestinal bleeding and hemorrhagic stroke).

Furthermore, despite evidence of the efficacy of aspirin in secondary prevention, its use in patients at high risk of strokes and heart attacks remains suboptimal (11). A possible explanation for this underuse may be concern about the relative benefit in relation to the potential risk for serious hemorrhagic events. Accurate evaluation of the benefits and harms of aspirin is therefore warranted.

Two meta-analyses have provided some information. The first examined the benefit and harms of aspirin in subjects without known cardiovascular or cerebrovascular disease (primary prevention) (12). The authors selected articles published between 1966 and 2000—five large controlled studies of primary prevention that lasted at least 1 year and nine studies of the effects of aspirin on gastrointestinal bleeding and hemorrhagic stroke. The five randomized, placebo-controlled trials included more than 50 000 patients and the meta-analysis showed that aspirin significantly reduced the risk of the combined outcome (confirmed non-fatal myocardial infarction or death from coronary heart disease) (OR = 0.72; 95% CI = 0.60, 0.87). However, aspirin increased the risk of major gastrointestinal bleeding (OR = 1.7; CI = 1.4, 2.1) significantly, while the small

increase found for hemorrhagic stroke (OR = 1.4; CI = 0.9, 2.0) was not statistically significant. All-cause mortality was not significantly affected (OR = 0.93; CI = 0.84; 1.02). Most important was the finding that the net effect of aspirin improved with increasing risk of coronary heart disease. The meta-analysis showed that for 1000 patients with a 5% risk of coronary heart disease events over 5 years, aspirin would prevent 6–20 myocardial infarctions but would cause also 0–2 hemorrhagic strokes and 2–4 major gastrointestinal bleeds. For patients at lower risk (1% over 5 years), aspirin would prevent 1–4 myocardial infarctions but would still cause 0–2 hemorrhagic strokes and 2-4 major gastrointestinal bleeds.

Therefore when deciding to use aspirin in primary prophylaxis, one should take account of the relative utility of the different outcomes that are prevented or caused by aspirin.

The other meta-analysis (13) compared the benefits of aspirin in secondary prevention with the risk of gastrointestinal bleeding. An earlier analysis of this problem included patients at various levels of risk and doses of aspirin that would currently be regarded as too high (14), and may therefore have either underrepresented the benefit or exaggerated the risk. In another analysis there was no difference in the risk of gastrointestinal bleeding across the whole range of doses used (15).

The meta-analysis reviewed all randomized, placebo-controlled, secondary prevention trials of at least 3-months duration published from 1970 to 2000. The dosage of aspirin was 50–325 mg/day. Six studies contributed 6300 patients to the analysis (3127 on aspirin and 3173 on placebo). Aspirin reduced all-cause mortality by 18%, the number of strokes by 20%, myocardial infarctions by 30%, and other vascular events by 30%. On the other hand, patients who took aspirin were 2.5 times more likely than those who took placebo to have gastrointestinal tract bleeds. The number of patients needed to be treated (NNT) to prevent one death from any cause was 67 and the NNT to cause one gastrointestinal bleeding event was 100. In other words 1.5 lives can be saved for every gastrointestinal bleed attributed to aspirin. Although the risk of gastrointestinal bleeding was increased by aspirin, the hemorrhagic events were manageable and led to no deaths. On the basis of these data we can conclude that the benefits–harm balance for low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events is highly favorable. The same conclusions have been drawn from the systematic overview published by the Antithrombotic Trialists Collaboration Group, which analysed data from 287 studies involving 135 000 patients (16).

As far as primary prevention of cardiovascular events is concerned, it appears that aspirin can reduce heart attacks and strokes but increases gastrointestinal and intracranial bleeding. The decision to use aspirin in primary prevention should therefore take into account the fact that the net effect of aspirin improves with increasing risk of coronary heart disease as well as the values that patients attach to the main favorable and unfavorable outcomes.

Organs and Systems

Cardiovascular

Apart from rare reports of variant angina pectoris and vasculitis theoretically related to thromboxane, aspirin is not associated with adverse effects on the cardiovascular system (17,18), except an increase in circulating plasma volume after large doses.

Respiratory

The effect of aspirin on bronchial musculature is discussed in the section on Immunologic in this monograph.

Salicylates can cause pulmonary edema, particularly in the elderly, especially if they are or have been heavy smokers (19).

Chronic salicylate toxicity can cause pulmonary injury, leading to respiratory distress. Lung biopsy may show diffuse alveolar damage and fibrosis (20).

Nervous system

Salicylism is a reaction to very high circulating concentrations of salicylate, characterized by tinnitus, dizziness, confusion, and headache.

Encephalopathy secondary to hyperammonemia has been reported in those rare cases of liver failure that are associated with high doses of aspirin, and this also forms a major feature of Reye's syndrome (see the section on Liver in this monograph).

One case-control study showed no increased risk of intracerebral hemorrhage in patients using aspirin or other NSAIDs in low dosages as prophylaxis against thrombosis (21). However, intracerebral hemorrhage has been reported with aspirin, even in low doses, and in the SALT study (22) and the Physicians Health Study of 1989 (23) hemorrhagic stroke and associated deaths occurred with aspirin.

Sensory systems

Eyes

Well-documented acute myopia and increased ocular pressure attributed to aspirin has been described (24).

Ears

With the high concentrations achieved in attempted suicide, tinnitus and hearing loss, leading to deafness, develop within about 5 hours, usually with regression within 48 hours, but permanent damage can occur. Disturbed balance, often with vertigo, can develop, as well as nausea, usually with maintenance of consciousness, even without treatment. It has been postulated that in this state depolarization of the cochlear hair cells occurs, similar to the changes induced by pressure. Tinnitus is also a symptom of salicylism.

Metabolism

Aspirin lowers plasma glucose concentrations in C-peptide-positive diabetic subjects and in normoglycemic persons (25). This is of no clinical significance.

Fluid balance

NSAIDs can cause fluid retention, but this has rarely been reported with aspirin.

- Severe fluid retention, possibly due to impaired renal tubular secretion, has been reported in a 29-year-old woman taking aspirin (1.5 g/day for several days) for persistent headache (26). During rechallenge with aspirin (0.5 g tds for 3 days) a dynamic renal scintigram showed a substantial fall in tubular filtration. Withdrawal was followed by complete uneventful recovery.

Pulmonary edema is a feature of salicylate intoxication, but this patient was taking a therapeutic dosage.

Hematologic

Thrombocytopenia, agranulocytosis, neutropenia, aplastic anemia, and even pancytopenia have been reported in association with aspirin. The prospect for recovery from the latter is poor, mortality approaching 50%.

Hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase deficiency or erythrocyte glutathione peroxidase deficiency (SED-9, 128) (27–29). Whether these reports have anything more than anecdotal value (SEDA-17, 97) is not known.

Simple iron deficiency caused by occult blood loss occurs with a frequency of 1%, and upper gastrointestinal bleeding resulting from regular aspirin ingestion is the reason for hospitalization in about 15 patients per 100 000 aspirin users per year. Aspirin causes bleeding of sufficient severity to lead to iron deficiency anemia in 10–15% of patients taking it continuously for chronic arthritis. Some individuals are particularly at risk because of pregnancy, age, inadequate diet, menorrhagia, gastrectomy, or malabsorption syndromes.

Macrocytic anemia associated with folate deficiency has been described in patients with rheumatoid arthritis (30) and also in patients who abuse analgesic mixtures containing aspirin (30).

Effects on coagulation

Aspirin in high doses for several days can reduce prothrombin concentrations and prolong the prothrombin time. This will contribute to bleeding problems initiated by other factors, including aspirin's local irritant effects on epithelial cells. It is therefore very risky to use aspirin in patients with bleeding disorders. The effect will contribute to increased blood loss at parturition, spontaneous abortion, or menorrhagia, and may be linked to persistent ocular hemorrhage, particularly in older people, with or without associated surgical intervention (31,32).

By virtue of its effects on both cyclo-oxygenase isoenzymes, aspirin inhibits platelet thromboxane A_2 formation. This effect in the platelet is irreversible and will persist for the lifetime of the platelet (that is up to 10 days), since the platelet cannot synthesize new cyclo-oxygenase. It is of clinical significance that the dose of aspirin necessary to inhibit platelet thromboxane A_2 (around 40 mg/day) is much lower than that needed to inactivate the subendothelial prostacyclin (PGI_2). Hence, platelet aggregation is inhibited, with some associated dilatation of coronary and cerebral arterioles, at doses that do not interfere with prostacyclin inhibition. It is important, in considering the dosage of aspirin for prophylaxis (see below), to appreciate that prostacyclin is a general inhibitor of platelet aggregation, while aspirin, as a cyclo-oxygenase inhibitor, affects aggregation from a limited number of stimuli, for example ADP, adrenaline, thromboxane A_2. It is also worth recalling that the vascular endothelium can synthesize new cyclo-oxygenase, so that any effect on prostacyclin synthesis is of limited duration only (SEDA-12, 74) (33).

Several long-term studies have been carried out since the 1980s to determine the prophylactic usefulness of these effects on clotting. It is now clear that aspirin in dosages of around 300 mg/day can be used successfully for secondary prophylaxis in patients with coronary artery disease, in order to reduce the incidence of severe myocardial infarction, and in patients with cerebrovascular disease to reduce the incidence of transient ischemic attacks and strokes. There is some suggestion that higher doses of aspirin may be required in women. A major drawback has been the high incidence of gastrointestinal adverse effects and particularly bleeding in aspirin-treated groups (5,6,10,34). In view of the age group involved, bleeding can have serious implications. In an attempt to avoid this high proportion of ill-effects and yet retain the benefits of prophylactic antithrombotic treatment, a few trials have been conducted using aspirin in a dose of 162 mg (ISIS-2) (35) and 75 mg (RISC) (36) in symptomatic coronary heart disease, with good evidence of efficacy. Two studies have been reported in patients with cerebrovascular events, namely the Dutch TIA trial with aspirin 30 versus 283 mg (21) and the SALT study with aspirin 75 mg (22). The former did not show any difference in efficacy between the 30 and 283 mg dose groups, but there was no placebo control. The latter study showed a significant reduction in thrombotic stroke. However, intracerebral hemorrhage has been reported with aspirin, even in low doses, and in this as well as in the Physicians Health Study of 1989 (23), hemorrhagic stroke and associated deaths occurred with aspirin. On the other hand, the incidence of serious gastrointestinal events was much lower than previously described.

As nearly all of the risks seem to be dose-related (SEDA-21, 96), there is a good prospect that an even lower daily dose of aspirin may offer advantages in antithrombotic prophylaxis without an increased risk of bleeding, but the results of further such studies are still awaited (9).

Relatively few patients developed a prolonged bleeding time while taking aspirin or other NSAIDs and only few had significant intraoperative blood loss. There is variation in the response of patients for unknown reasons and so the recommendation that NSAIDs should be withdrawn before elective surgery awaits confirmation (SEDA-19, 96).

Gastrointestinal

Gastric ulceration and hemorrhage

DoTS classification

Dose-relation: collateral effect
Time-course: intermediate
Susceptibility factors: age (over 65); sex (women); disease (peptic ulceration)

The gastrointestinal adverse effects of aspirin and the other NSAIDs are the most common. While some argue against a causative relation between aspirin ingestion and chronic gastric ulceration, the current consensus favors such a relation, while admitting that other factors, such as *Helicobacter pylori*, are likely to play a part. Patients aged over 65 years and women are more at risk, as are those who take aspirin over prolonged periods in a daily dose of about 2 g or more.

However, there is no ambiguity about the association of aspirin with gastritis, gastric erosions, or extensions of existing peptic ulcers, all of which are demonstrable by endoscopy. Even after one or two doses, superficial erosions have been described in over 50% of healthy subjects. This association is now almost universally accepted as the standard basis for comparative testing of NSAIDs and other drugs (21,37–39). Whether it is of benefit to use other drugs concomitantly to prevent the effect of gastric acid on the mucosa, and thus reduce the risk of gastric ulceration, is discussed further in this monograph.

Dyspepsia, nausea, and vomiting occur in 2–6% of patients after aspirin ingestion. Patients with rheumatoid arthritis seem to be more sensitive, and the frequency of aspirin-induced dyspepsia in this group is 10–30% (SEDA-9, 129). However, these symptoms are generally poor predictors of the incidence of mucosal damage (SEDA-18, 90).

The bleeding that occurs is usually triggered by erosions and aggravated by the antithrombotic action of aspirin. While it is reported to occur in up to 100% of regular aspirin takers, bleeding tends to be asymptomatic in young adults, unless it is associated with peptic ulceration, but it is readily detectable by endoscopy and the presence of occult blood in the feces. Hematemesis and melena are less often seen, the odds ratio being 1.5–2.0 in an overview of 21 low-dose aspirin prevention studies (40). A degree of resultant iron deficiency anemia is common. Such events are more commonly seen in older people in whom there is a significant proportion of serious bleeding and even deaths. Major gastrointestinal bleeding has an incidence of 15 per 100 000 so-called heavy aspirin users. However, the interpretation of "heavy" and of quantities of aspirin actually taken is to a large extent subjective and very dependent on the questionable accuracy of patient reporting. The risk appears to be greater in women, smokers, and patients concurrently taking other NSAIDs, and is possibly affected by other factors not yet established (41). Gastrointestinal perforation can occur without prodromes. Aspirin increases the risk of major upper gastrointestinal bleeding and perforation two- to three-fold in a dose-related manner, but deaths are rare.

Incidence

Of the estimated annual 65 000 upper gastrointestinal emergency admissions in the UK, nearly 20% (including deaths in 3.4%) are attributable to the use of prostaglandin synthesis inhibitors (42). As might be expected with an inhibitor of prostaglandin synthesis, the cytoprotective effects of prostaglandin E and prostacyclin (PGI_2) are reduced by aspirin, as is the inhibitory action on gastric acid secretion. This effect may be both direct, as is the case with aspirin released in the stomach (or the lower rectum in the case of aspirin suppositories), and indirect following absorption and distribution via the systemic circulation; attempts to reduce the problems by coating and buffering can therefore have only limited success. The indirect type of effect is shown by the fact that these adverse gastric effects can also be exerted by parenteral lysine acetylsalicylate (SEDA-10, 72). The local effects depend in part on the tablet particle size, solubility, and rate of gastric absorption, while the most important variable appears to be gastric pH. On the other hand, within-day changes in the pharmacokinetics of the analgesic compounds may be involved in the prevalence of gastrointestinal adverse effects.

The estimates of gastrointestinal complication rates from aspirin are generally derived from clinical trials (SEDA-21, 100). However, the applicability of the results of such trials to the general population may be debatable, as protocols for these studies often are designed precisely to avoid enrollment of patients who are at risk of complications. Indeed differences in benefit-to-harm balance have been found in trials using the same dose of aspirin (43,44). For this reason, a population-based historical cohort study on frequency of major complications of aspirin used for secondary stroke prevention may be of interest (45). The study identified 588 patients who had a first ischemic stroke, transient ischemic attack, or amaurosis fugax during the study period. Of these, 339 patients had taken aspirin for an average of 1.7 years. The mean age of patients who had taken aspirin was 74 years. Complications occurred within 30 days of initiation of treatment in one patient, between 30 days and 6 months in 10 patients, between 6 months and 1 year in seven patients, and between 1 year and 2 years in two patients. Estimated standardized morbidity ratio of gastrointestinal hemorrhage (determined on the basis of 10 observed events and 0.661 expected events, during 576 person-years of observation) was 15 (95% CI = 7, 28). The estimated standardized morbidity ratio of intracerebral hemorrhage (determined on the basis of only one event and 0.59 expected events) was 1.7 (CI = 0.04, 9.4). One patient had a fatal gastrointestinal hemorrhage. Unfortunately these complication rates must be considered estimates, because aspirin therapy was not consistently recorded. However, the rates of complications were similar to those observed in some randomized clinical trials. On the basis of these data and of those of a meta-analysis of 16 trials involving more than 95 000 patients (45), the overall benefits of aspirin, measured in terms of preventing myocardial infarction and ischemic stroke, clearly outweigh the risks.

Dose-relatedness

The question of whether the risk of gastrointestinal hemorrhage with long-term aspirin is related to dose within the usual therapeutic dosage range (SEDA-12, 100) (15,46) merits attention. In a meta-analysis of the incidence of gastrointestinal hemorrhage associated with

long-term aspirin and the effect of dose in 24 randomized, controlled clinical trials including almost 66 000 patients exposed for an average duration of 28 months to a wide range of different doses of aspirin (50–1500 mg/day), gastrointestinal hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (OR = 1.68; 95% CI = 1.51, 1.88). In patients taking low doses of aspirin (50–162.5 mg/day; $n = 49\ 927$), gastrointestinal hemorrhage occurred in 2.3% compared with 1.45% taking placebo (OR = 1.56; 95% CI = 1.40, 1.81). The pooled OR for gastrointestinal hemorrhage with low-dose aspirin was 1.59 (95% CI = 1.4, 1.81). A meta-regression to test for a linear relation between the daily dose of aspirin and the risk of gastrointestinal hemorrhage gave a pooled OR of 1.015 (95% CI = 0.998, 1.047) per 100 mg dose reduction. The reduction in the incidence of gastrointestinal hemorrhage was estimated to be 1.5% per 100 mg dose reduction, but this was not significant.

These data are in apparent contrast with others previously reported (SEDA-21, 100) (14), which showed that gastrointestinal hemorrhage was related to dose in the usual dosage range. Many reasons may explain these contrasting results, the most important being differences in the definition of the hemorrhagic events, in study design, in the population studied, and in the presence of accessory risk factors (47–49).

The recent trends toward the use of lower doses of aspirin have been driven by the belief that these offer a better safety profile while retaining equivalent therapeutic efficacy. Despite the large number of patients enrolled in randomized clinical trials and included in meta-analyses, there is no firm evidence that dose reduction significantly lowers the risk of gastrointestinal bleeding. Patients and doctors therefore need to consider the trade-off between the benefits and harms of long-term treatment with aspirin. Meanwhile, it seems wise to use the lowest dose of proven efficacy.

A systematic review of 17 epidemiological studies conducted between 1990 and 2001 has provided further data on this topic (50). The effect of aspirin dosage was investigated in five studies. There was a greater risk of gastrointestinal complications with aspirin in dosages over 300 mg/day than in dosages of 300 mg/day or less. However, users of low-dose aspirin still had a two-fold increased risk of such complications compared with non-users, with no clear evidence of a dose-response relation at dosages under 300 mg/day, confirming previous findings (15). The study also addressed the question of whether the aspirin formulation affects gastrotoxicity. The pooled relative risks of gastrointestinal complications in four studies were 2.4 (95%; CI = 1.9, 2.9) for enteric-coated aspirin, 5.3 (3.0, 9.2) for buffered formulations, and 2.6 (2.3, 2.9) for plain aspirin, compared with non-use. These data confirm those from previous studies (SEDA-21, 100) (15), which negate any protective effect of the most frequently used aspirin formulations. Furthermore, there were higher relative risks, compared with non-use, for gastrointestinal complications in patients who used aspirin regularly (RR = 3.2; CI = 2.6, 5.9) than in patients who used it occasionally (2.1; 1.7, 2.6), and during the first month of use (4.4; 3.2, 6.1) compared with subsequent months (2.6; 2.1, 3.1).

Comparative studies

A comparative study of gastrointestinal blood loss after aspirin 972 mg qds for 4 days versus different doses of piroxicam (20 mg od, 5 mg qds, and 10 mg qds) showed that piroxicam did not increase fecal blood loss, whereas aspirin did. Gastroscopic evidence of irritation was also greater with aspirin (51).

In a randomized trial comparing ticlopidine (500 mg/day) with aspirin (1300 mg/day) for the prevention of stroke in high-risk patients, the incidence of bleeding was similar in both groups, although more patients treated with aspirin developed peptic ulceration or gastrointestinal hemorrhage (52).

Risk factors

A study of the risk factors for gastrointestinal perforation, a much less frequent event than bleeding, has confirmed that aspirin and other NSAIDs increase the risk of both upper and lower gastrointestinal perforation (OR 6.7, CI 3.1–14.5 for NSAIDs) (53). Gastrointestinal perforation has been associated with other factors, such as coffee consumption, a history of peptic ulcer, and smoking. The combination of NSAIDs, smoking, and alcohol increased the risk of gastrointestinal perforation (OR 10.7, CI 3.8–30) (SEDA-21, 97).

Associated effects

Aspirin can also play a role in esophageal bleeding, ulceration, or benign stricture, and it should be considered as a possible cause in patients, particularly the elderly, who present with any of these features. There have also been reports of rectal stricture in the elderly, associated with the use of aspirin suppositories. Effects on both these strictures emphasize the significance of a direct local action of aspirin as well as a systemic action and underlines the relevance of the involvement of oxygen-derived free radicals in the pathogenesis of mucosal lesions in the gastrointestinal tract (54–56).

A gastrocolic fistula developed in a 47-year-old woman taking aspirin and prednisone for rheumatoid arthritis (57). Other similar case reports have been published (58,59).

Long-term effects

The effects on the stomach of continued exposure to aspirin remain controversial. While in short-term use, gastric mucosal erosions may often be recurrent but transient and comparatively trivial lesions, with longer administration there seems to be an increased risk of progression to ulceration.

Prophylaxis

Intravenous administration, or the use of enteric-coated formulations or modified-release products all appear to reduce the risk both of bleeding and more particularly of erosions/ulceration. However, because of the indirect effect noted above, such formulations do not eliminate the risk, although they may reduce the incidence of

gastric or duodenal ulcer, as may buffered aspirin (60,61).

Considerable attention in recent years has been directed toward the efficacy of using synthetic forms of PGE_2, histamine H_2 receptor antagonists, proton pump inhibitors, or antacids, either to heal peptic ulcers associated with use of prostaglandin inhibitors or more significantly to act prophylactically to protect against ulceration or bleeding associated with aspirin or the NSAIDs. With the exception of PGE_2, there is no convincing evidence to justify their prophylactic use, as they do not reduce the risk of significant gastrointestinal events. In contrast, their soothing effect on gastrointestinal symptoms may ultimately result in more severe complications (62). Since all these agents carry their own potential risks, it is more than questionable whether administration to a patient with normal gastrointestinal mucosa is justified. Generally, use of prostaglandin inhibitors should be limited to the shortest possible duration, thereby minimizing, but not eliminating, the risk of gastrointestinal damage. Only high-risk patients should be eligible for prophylactic drug therapy. Well-known risk factors for the development of mucosal lesions of the gastrointestinal tract are age (over 75 years), a history of peptic ulcer, or gastrointestinal bleeding, and concomitant cardiac disease.

Liver

Aspirin can cause dose-related focal hepatic necrosis that is usually asymptomatic or anicteric. Much of the evidence for hepatotoxicity of aspirin and the salicylates has been shown in children (63,64), usually in patients with connective tissue disorders, taking relatively high long-term dosages for Still's disease, rheumatoid arthritis, or occasionally systemic lupus erythematosus. Rises in serum transaminases seem to be the most common feature (in up to 50% of patients) and are usually reversible on withdrawal, but they occasionally lead to fatal hepatic necrosis. Severe and even fatal metabolic encephalopathy can also occur, as in Reye's syndrome (see the section on Reye's syndrome in this monograph). One can easily overload the young patient's individual metabolic capacity. The co-existence of hypoalbuminemia may be a particular risk factor; in patients with hypoalbuminemia of 35 g/l or less, close monitoring of the aspartate transaminase is advisable, especially if the concentration of total serum salicylate is 1.1 mmol/l or higher (65). Plasma salicylate concentrations in serious cases have usually been in excess of 1.4 mmol/l and liver function tests return rapidly to normal when the drug is withdrawn. Finally, a very small number of cases of chronic active hepatitis have been attributed to aspirin (66).

Reye's syndrome

First defined as a distinct syndrome in 1963, Reye's syndrome came to be regarded some years later as an adverse effect of aspirin. In fact, the position is more complex, and the syndrome still cannot be assigned a specific cause. There is general agreement that the disorder presents a few days after the prodrome of a viral illness. Well over a dozen different viruses have so far been implicated, including influenza A and B, adenovirus, *Varicella*, and reovirus. Various other factors have also been incriminated, including aflatoxins, certain pesticides, and such antioxidants as butylated hydroxytoluene. Only in the case of aspirin have some epidemiological studies been conducted, and these appeared to show a close correlation with cases of Reye's syndrome. It was these studies that led to regulatory action against the promotion of salicylate use in children. However, doubt has been thrown on the clarity of the link, and it now seems increasingly likely that while there is some association with aspirin, the etiology is in fact multifactorial, including some genetic predisposition. Studies in Japan did not support the US findings, while studies in Thailand and Canada invoked other factors.

Two characteristic phenomena are present in Reye's syndrome.

1. Damage to mitochondrial structures, with pleomorphism, disorganization of matrix, proliferation of smooth endoplasmic reticulum, and an increase in peroxisomes; mitochondrial enzyme activity is severely reduced, but cytoplasmic enzymes are unaffected. The changes first appear in single cells, but may spread to all hepatocytes. Recovery may be complete by 5–7 days. While these changes are most evident in liver cells, similar effects have been seen in cerebral neurons and skeletal muscle. There appears to be a block in beta-oxidation of fatty acids (inhibition of oxidation of NAB-linked substrates). In vitro aspirin selectively inhibits mitochondrial oxidation of medium- and long-chain fatty acids.
2. An acute catabolic state with hypoglycemia, hyperammonemia, raised activities of serum aspartate transaminase and creatine phosphokinase, and increased urinary nitrogen and serum long chain dicarboxylic acid.

Despite our lack of understanding of the syndrome, the decision taken in many countries to advise against the use of salicylates in children under 12 made an impact, in terms of a falling incidence of Reye's syndrome (SEDA-16, 96; SEDA-17, 97).

Over the last 25 years, in the USA, the incidence of Reye's syndrome has fallen significantly—from the time that the advice was introduced up to 1999 there were 25 reported cases, but 15 were in adolescents aged 12–17 years, and 8% of cases occurred in patients aged 15 years or over (67). In the UK, in view of these findings, the Commission on Safety of Medicines (CSM) amended its original statement and advised that aspirin should be avoided in febrile illnesses or viral infections in patients aged under 16 years. However, the appropriateness of this decision has been challenged (68). This is because the incidence of Reye's syndrome is already low and is falling; furthermore, restricting the use of aspirin leaves paracetamol and ibuprofen as the only available therapeutic alternatives, and their safety is not absolutely guaranteed and might be even worse than that of aspirin.

Urinary tract

Aspirin is associated with a small but significant risk of hospitalization for acute renal insufficiency (SEDA-19, 95).

When aspirin is used by patients on sodium restriction or with congestive heart failure, there tends to be a reduction in the glomerular filtration rate, with preservation of normal renal plasma flow. Some renal tubular epithelial shedding can also occur.

Severe systemic disease involving the heart, liver, or kidneys seems to predispose the patient to the effects of aspirin and other NSAIDs on renal function (69).

Chronic renal disease

Renal papillary necrosis has been reported after long-term intake or abuse of aspirin and other NSAIDs (SEDA-11, 85) (SEDA-12, 79). The relation between long-term heavy exposure to analgesics and the risk of chronic renal disease has been the object of intensive toxicological and epidemiological research for many years (SEDA-24, 120) (70). Most of the earlier reports suggested that phenacetin-containing analgesics probably cause renal papillary necrosis and interstitial nephritis. In contrast, there was no convincing epidemiological evidence that non-phenacetin-containing analgesics (including paracetamol, aspirin, mixtures of the two, and NSAIDs) cause chronic renal disease. Moreover, findings from epidemiological studies should be interpreted with caution, because of a number of inherent limitations and potential biases in study design (71). Two methodologically sound studies have provided information on this topic.

The first was the largest cohort study conducted thus far to assess the risk of renal dysfunction associated with analgesic use (72). Details of analgesic use were obtained from 11 032 men without previous renal dysfunction participating in the Physicians' Health Study (PHS), which lasted 14 years. The main outcome measure was a raised creatinine concentration defined as 1.5 mg/dl (133 μmol/l) or higher and a reduced creatinine clearance of 55 ml/minute or less. In all, 460 men (4.2%) had a raised creatinine concentration and 1258 (11%) had a reduced creatinine clearance. Mean creatinine concentrations and creatinine clearances were similar among men who did not use analgesics and those who did. This was true for all categories of analgesics (paracetamol and paracetamol-containing mixtures, aspirin and aspirin-containing mixtures, and other NSAIDs) and for higher-risk groups, such as those aged 60 years or over or those with hypertension or diabetes.

These data are convincing, as the large size of the PHS cohort should make it possible to examine and detect even modest associations between analgesic use and a risk of renal disease. Furthermore, this study included more individuals who reported extensive use of analgesics than any prior case-control study. However, the study had some limitations, the most important being the fact that the cohort was composed of relatively healthy men, most of whom were white. These results cannot therefore be generalized to the entire population. However, the study clearly showed that there is not a strong association between chronic analgesic use and chronic renal dysfunction among a large cohort of men without a history of renal impairment.

The second study was a Swedish nationwide, population-based, case-control study of early-stage chronic renal insufficiency in men whose serum creatinine concentration exceeded 3.4 mg/dl (300 μmol/l) or women whose serum creatinine exceeded 2.8 mg/dl (250 μmol/l) (73). In all, 918 patients with newly diagnosed renal insufficiency and 980 controls were interviewed and completed questionnaires about their lifetime consumption of analgesics. Compared with controls, more patients with chronic renal insufficiency were regular users of aspirin (37 versus 19%) or paracetamol (25 versus 12%). Among subjects who did not use aspirin regularly, the regular use of paracetamol was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of paracetamol. The risk increased with increasing cumulative lifetime dose. Patients who took 500 g or more over a year (1.4 g/day) during periods of regular use had an increased odds ratio for chronic renal insufficiency (OR = 5.3; 95% CI = 1.8, 15). Among subjects who did not use paracetamol regularly, the regular use of aspirin was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of aspirin. The risk increased significantly with an increasing cumulative lifetime dose of aspirin. Among the patients with an average intake of 500 g or more of aspirin per year during periods of regular use, the risk of chronic renal insufficiency was increased about three-fold (OR = 3.3; CI = 1.4, 8.0). Among patients who used paracetamol in addition to aspirin, the risk of chronic renal insufficiency was increased about two-fold when regular aspirin users served as the reference group (OR = 2.2; CI = 1.4, 3.5) and non-significantly when regular paracetamol users were used as controls (OR = 1.6; CI = 0.9, 2.7). There was no relation between the use of other analgesics (propoxyphene, NSAIDs, codeine, and pyrazolones) and the risk of chronic renal insufficiency. Thus, the regular use of paracetamol, or aspirin, or both was associated dose-dependently with an increased risk of chronic renal insufficiency. The OR among regular users exceeded 1.0 for all types of chronic renal insufficiency, albeit not always significantly. These results are consistent with exacerbating effects of paracetamol and aspirin on chronic renal insufficiency, regardless of accompanying disease.

How can we explain the contrasting results of these two studies? A possible explanation lies in the different populations studied. In the PHS study, relatively healthy individuals were enrolled while in the Swedish study all the patients had pre-existing severe renal or systemic disease, suggesting that such disease has an important role in causing analgesic-associated chronic renal insufficiency. People without pre-existing disease who use analgesics may have only a small risk of end-stage renal disease.

Skin

Hypersensitivity reactions, such as urticaria and angioedema, are relatively common in subjects with aspirin hypersensitivity. Purpura, hemorrhagic vasculitis, erythema multiforme, Stevens–Johnson syndrome, and Lyell's syndrome have also been reported, but much less often. Fixed drug eruptions, probably hypersensitive in origin, are periodically described. In some patients they do not recur on rechallenge, that is the sensitivity disappears (74).

Musculoskeletal

There is evidence that salicylates together with at least some NSAIDs suppress proteoglycan biosynthesis independently of effects on prostaglandin synthesis (75). Thus, prolonged use of these agents can accentuate deterioration of articular cartilage in weight-bearing arthritic joints. If this is proved, the problem will be of greatest relevance to elderly people with osteoarthritis, a condition in which this use of prostaglandin inhibitors is questionable.

Immunologic

Aspirin hypersensitivity

Of adult asthmatics 2–20% have aspirin hypersensitivity (9). The mechanism is related to a deficiency in bronchodilator prostaglandins; prostaglandin inhibition may make arachidonic acid produce more leukotrienes with bronchoconstrictor activity. Oral challenge in asthmatic patients is an effective but potentially dangerous method for establishing the presence of aspirin hypersensitivity (63).

The term "aspirin allergy" is better avoided, in the absence of identification of a definite antigen–antibody reaction. This topic has been reviewed (SEDA-17, 94) (SEDA-18, 90).

Epidemiology

Aspirin hypersensitivity is relatively common in adults (about 20%). Estimates of the prevalence of aspirin-induced asthma vary from 3.3 to 44% in different reports (SEDA-5, 169), although it is often only demonstrable by challenge tests with spirometry, and only 4% have problems in practice. Patients with existing asthma and nasal polyps or chronic urticaria have a greater frequency of hypersensitivity (76), and women appear to be more susceptible than men, perhaps particularly during the childbearing period of life (77). Acute intolerance to aspirin can develop even in patients who have taken the drug for some years without problems.

There is considerable cross-reactivity with other NSAIDs and the now widely banned food colorant tartrazine (78). Cross-sensitization between aspirin and tartrazine is common; for example, in one series 24% of aspirin-sensitive patients also reacted to tartrazine (SEDA-9, 76).

Mechanism

The current theory of the mechanism relates to the inhibition of cyclo-oxygenases (79) and a greater degree of interference with PGE_2 synthesis, allowing the bronchoconstrictor PGF_2 to predominate in susceptible individuals.

PGE_2 inhibition in macrophages may also unleash bronchial cytotoxic lymphocytes, generated by chronic viral infection, leading to destruction of virus-infected cells in the respiratory tract (80). When urticaria occurs, it may result from increased release of leukotrienes LTC_4, D_4, and E_4, which also induces bronchoconstriction, with a shunt of arachidonic acid toward lipoxygenation in aspirin-sensitive asthmatics (SEDA-18, 93). Aspirin-induced asthma patients show hyper-reactivity to inhaled metacholine and sulpyrine.

Features

The features of aspirin hypersensitivity include bronchospasm, acute and usually generalized urticaria, angioedema, severe rhinitis, and shock. These reactions can occur alone or in various combinations, developing within minutes or a few hours of aspirin ingestion, and lasting until elimination is complete. They can be life-threatening. The bronchospastic type of reaction predominates in adults, only the urticarial type being found in children. The frequency of recurrent urticaria is significantly greater in adults (3.8 versus 0.3%).

People with asthma may be particularly sensitive to acetylsalicylic acid, which may be given alone or as a constituent of a combination medicine. The association between aspirin sensitivity, nasal polyps, and rhinitis in asthma is well known.

Henoch–Schönlein purpura has been reported (81).

Life-threatening respiratory distress, facial edema, and lethargy occurred in a woman with a history of severe asthma and aspirin hypersensitivity (SEDA-22, 118).

Aspirin-sensitive subjects may have attacks induced by other NSAIDs (82).

Fish oil can also cause exacerbation of asthma in aspirin-sensitive patients (83).

Prophylaxis and treatment

Asthma induced by aspirin is often severe and resistant to treatment. Avoidance of aspirin and substances to which there is cross-sensitivity is the only satisfactory solution. Desensitization is not usually successful and repeated treatments are needed to maintain any effect (84,85).

Long-Term Effects

Tumorigenicity

Studies on the tumor-inducing effects of heavy use of analgesics, especially those that contain phenacetin, have given contrasting results (SEDA-21, 100) (86,87). There has been a case-control study of the role of habitual intake of aspirin on the occurrence of urothelial cancer and renal cell carcinoma (88). In previous studies there was a consistent association between phenacetin and renal cell carcinoma, but inconclusive results with respect to non-phenacetin analgesics. In 1024 patients with renal cell carcinoma and an equal number of matched controls, regular use of analgesics was a significant risk factor for renal cell carcinoma (OR = 1.6; CI = 1.4, 1.9). The risk was significantly increased by aspirin, NSAIDs, paracetamol, and phenacetin, and within each class of analgesic the risk increased with increasing exposure. Individuals in the highest exposure categories had about a 2.5-fold increase in risk relative to non-users or irregular users of analgesics. However, exclusive users of aspirin who took aspirin 325 mg/day or less for cardiovascular problems were not at an increased risk of renal cell carcinoma (OR = 0.9; CI = 0.6, 1.4).

Second-Generation Effects

Teratogenicity

It is perhaps surprising that aspirin, which is teratogenic in rodents, and which by virtue of its capacity to inhibit prostaglandin synthesis would be expected to affect the development of the renal and cardiovascular systems, has shown no evidence of teratogenesis in humans, despite very widespread use in pregnant women. Perhaps increased production of prostaglandins during pregnancy overrides the effects of aspirin in the usual dosages, and the intervention of placental metabolism protects the human fetus from exposure to aspirin. Whatever the explanation, there are very few reports in which aspirin can be implicated as a human teratogen and a few studies (89,90) have provided positive reassurance.

Fetotoxicity

Because aspirin is an antithrombotic agent and can promote bleeding, it should be avoided in the third trimester of pregnancy and at parturition (91). At parturition there is a second reason for avoiding aspirin, since its prostaglandin-inhibiting capacity could mean that it will delay parturition and induce early closure of the ductus arteriosus in the near-term fetus, as other NSAIDs do (92). However, its use in low doses in pregnancy may prevent retardation of fetal growth (93).

Susceptibility Factors

Age

In view of the association with Reye's syndrome, aspirin should be avoided in children aged under 16.

Drug Administration

Drug formulations

Although the use of enteric-coated aspirin can reduce its direct adverse effect on the stomach (SEDA-10, 72), it could in principle transfer these to some extent to the intestine; modified-release NSAIDs have sometimes caused intestinal perforation.

Enteric coating reduces the rate of absorption of aspirin. In cases of severe overdosage this can cause difficulties in diagnosis and treatment, since early plasma salicylate measurements are unreliable, maximum blood concentrations sometimes not being reached until 60 or 70 hours after overdose (94,95). Another complication of the use of enteric-coated aspirin is the risk of gastric outlet obstruction and the resulting accumulation of tablets because of subclinical pyloric stenosis.

Drug overdose

Acute poisoning

Acute salicylate poisoning is a major clinical hazard (96), although it is associated with low major morbidity and mortality, in contrast to chronic intoxication (SEDA-17, 98). It can cause alkalemia or acidemia, alkaluria or aciduria, hyperglycemia or hypoglycemia, and water and electrolyte imbalances. However, the usual picture is one of hypokalemia with metabolic acidosis and respiratory alkalosis. Effects on hearing have been referred to in the section on Sensory systems in this monograph. Nausea, vomiting, tinnitus, hyperpnea, hyperpyrexia, confusion, disorientation, dizziness, coma, and/or convulsions are common. They are expressions of the nervous system effects of the salicylates. Gastrointestinal hemorrhage is frequent.

Serum salicylate concentrations above 3.6 mmol/l are likely to be toxic, and concentrations of 5.4 mmol/l can easily prove fatal.

After ingestion, drug absorption can be prevented by induction of emesis, gastric lavage, and the administration of active charcoal; drug excretion is enhanced by administering intravenous alkalinizing solutions, hemoperfusion, and hemodialysis (97). Forced diuresis is dangerous and unnecessary.

Fluid and electrolyte management is the mainstay of therapy. The immediate aim must be to correct acidosis, hyperpyrexia, hypokalemia, and dehydration. In severe cases vitamin K_1 should be given to counteract hypoprothrombinemia.

Chronic poisoning

Chronic salicylate intoxication is commonly associated with chronic daily headaches, lethargy, confusion, or coma. Since headache is a feature, it can easily be misdiagnosed if the physician is not aware that aspirin has been over-used. Depression of mental status is usually present at the time of diagnosis, when the serum salicylate concentration is at a peak. The explanation of depression, manifested by irritability, lethargy, and unresponsiveness, occurring 1–3 days after the start of therapy for aspirin intoxication, lies in a persistently high concentration of salicylate in the central nervous system, while the serum salicylate concentration falls to non-toxic values. The delayed unresponsiveness associated with salicylate intoxication appears to be closely associated with the development of cerebral edema of uncertain cause. The encephalopathy that ensues appears to be directly related to increased intracranial pressure, a known effect of prostaglandin synthesis inhibitors; it responds to mannitol (98).

Drug–Drug Interactions

Alcohol

Although ethanol itself has no effect on bleeding time, it enhances the effect of aspirin when given simultaneously or up to at least 36 hours after aspirin ingestion (99). Ethanol also promotes gastric bleeding.

The FDA has announced its intention to require alcohol warnings on all over-the-counter pain medications that contain acetylsalicylic acid, salicylates, paracetamol, ibuprofen, ketoprofen, or naproxen. The proposed warnings are aimed at alerting consumers to the specific risks incurred from heavy alcohol consumption and its interaction with analgesics. For products

that contain paracetamol, the warning indicates the risks of liver damage in those who drink more than three alcoholic beverages a day. For formulations that contain salicylates or the mentioned NSAIDs, three or more alcoholic beverages will increase the risk of stomach bleeding (100).

Anticoagulants

The effects on coagulation are additive if aspirin is used concurrently with anticoagulants. There are also other interaction mechanisms: the effect of the coumarins is temporarily increased by protein binding displacement, and if aspirin causes gastric hemorrhages, the latter may well be more severe when anticoagulants are being given.

Aspirin should therefore generally be avoided in patients adequately treated with anticoagulants. The most relevant information on hemorrhagic complications occurring during prophylaxis with antiplatelet drugs, whether used singly or in combination, has been provided by well-controlled prospective trials with aspirin (17), aspirin combined with dipyridamole (101), or aspirin compared with oral anticoagulants (102).

Antihypertensive drugs

An increase in mean supine blood pressure has been reported with aspirin (SEDA-19, 92). Aspirin may therefore interfere with antihypertensive pharmacotherapy, warranting caution, especially in the elderly.

Captopril

Aspirin is thought to reduce the antihypertensive effect of captopril (103).

Carbonic anhydrase inhibitors

In two children, aspirin potentiated the slight metabolic acidosis induced by carbonic anhydrase inhibitors (SEDA-9, 79) (104).

Glucocorticoids

The effects of aspirin on gastrointestinal mucosa will lead to additive effects if it is used concurrently with other drugs that have an irritant effect on the stomach, notably other NSAIDs or glucocorticoids (105,106).

Heparin

Risk factors for heparin-induced bleeding include concomitant use of aspirin (107).

Intrauterine contraceptive devices

The supposed mechanisms of action of intrauterine contraceptive devices (IUCDs) include a local inflammatory response and increased local production of prostaglandins that prevent sperm from fertilizing ova (108,109). As aspirin has both anti-inflammatory and antiprostaglandin properties, the contraceptive effectiveness of an IUCD can be reduced by the drug, although the effect on periodic bleeding may prevail.

Methotrexate

Aspirin displaces methotrexate from its binding sites and also inhibits its renal tubular elimination, so that the dosage of concurrently used methotrexate should be reduced (except once-a-week low-dose treatment in rheumatoid arthritis) (110).

Nitrates

Aspirin in low dosages (under 300 mg/day) is widely used in cardiovascular prophylaxis, but its use is accompanied by an increased risk of gastrointestinal bleeding (SEDA-21, 100). Of particular interest therefore are data from a retrospective case-control study showing that nitrate therapy may reduce the risk of aspirin-induced gastrointestinal bleeding (111). As nitrates are often used in the same population of patients, such data merit further confirmation from larger prospective studies.

NSAIDs

The effects of aspirin on gastrointestinal mucosa will lead to additive effects if it is used concurrently with other drugs that have an irritant effect on the stomach, notably other NSAIDs or glucocorticoids (105,106). Salicylates can be displaced from binding sites by some NSAIDs such as naproxen, or in turn displace others such as piroxicam.

Sodium valproate

Aspirin displaces sodium valproate from protein binding sites (112) and reduces its hepatic metabolism (113).

Streptokinase

Major hemorrhagic complications, including cerebral hemorrhage, can occur with aspirin (SEDA-23, 116) and the same is also true for thrombolytic therapy of acute ischemic stroke (114). A post hoc analysis of the Multicenter Acute Stroke Trial in Italy showed a negative interaction of aspirin and streptokinase in acute ischemic stroke (115). In 156 patients who received streptokinase plus aspirin and 157 patients treated with streptokinase alone, the combined regimen significantly increased early case fatality at days 3–10 (53 versus 30; OR = 2.5; CI = 1.2, 3.6). The excess in deaths was solely due to treatment and was not explained by the main prognostic predictors. Deaths in the combination group were mainly cerebral (42 versus 24; OR = 2.0; CI = 1.3, 3.7) and associated with hemorrhagic transformation (22 versus 11; OR = 2.2; CI = 1.0, 5.0). The data suggest that aspirin should be avoided when thrombolytic agents are used for acute ischemic stroke.

Uricosuric drugs

In low dosages (up to 2 g/day), aspirin reduces urate excretion and blocks the effects of probenecid and other uricosuric agents (116). However, in 11 patients with gout, aspirin 325 mg/day had no effect on the uricosuric action of probenecid (117). In higher dosages (over 5 g/day), salicylates increase urate excretion and inhibit the effects

of spironolactone, but it is not clear that these phenomena are of importance.

Food-Drug Interactions

Food allergens

Aspirin seems to potentiate the effects of food allergens, but this is uncertain (SEDA-10, 72).

Interference with Diagnostic Tests

Thyroid function tests

Through competitive binding to thyroid-binding globulin, salicylates in high concentrations can displace thyroxine and triiodothyronine, thus interfering with the results of diagnostic thyroid function tests (118).

References

1. MacIntyre A, Gray JD, Gorelick M, Renton K. Salicylate and acetaminophen in donated blood. CMAJ 1986; 135(3):215–16.
2. Wynne HA, Long A. Patient awareness of the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs). Br J Clin Pharmacol 1996;42(2):253–6.
3. National Drugs Advisory Board. Availability of aspirin and paracetamol. Annual Report 1987:24.
4. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci USA 1993;90(24):11693–7.
5. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. BMJ (Clin Res Ed) 1988;296(6618):320–31.
6. Hennekens CH, Buring JE, Sandercock P, Collins R, Peto R. Aspirin and other antiplatelet agents in the secondary and primary prevention of cardiovascular disease. Circulation 1989;80(4):749–56.
7. Macdonald R. Aspirin and extradural blocks. Br J Anaesth 1991;66(1):1–3.
8. de Swiet M, Redman CW. Aspirin, extradural anaesthesia and the MRC Collaborative Low-dose Aspirin Study in Pregnancy (CLASP). Br J Anaesth 1992;69(1):109–10.
9. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321(3):129–35.
10. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ (Clin Res Ed) 1988; 296(6618):313–16.
11. Stafford RS. Aspirin use is low among United States outpatients with coronary artery disease. Circulation 2000;101(10):1097–101.
12. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;136(2):161–72.
13. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med 2002;162(19):2197–202.
14. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. Br J Clin Pharmacol 1993;35(3):219–26.
15. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ 2000;321(7270):1183–7.
16. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71–86.
17. Aspirin Myocardial Infarction Study Research Group. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980;243(7):661–9.
18. Habbab MA, Szwed SA, Haft JI. Is coronary arterial spasm part of the aspirin-induced asthma syndrome? Chest 1986;90(1):141–3.
19. Heffner JE, Sahn SA. Salicylate-induced pulmonary edema. Clinical features and prognosis. Ann Intern Med 1981;95(4):405–9.
20. Grabe DW, Manley HJ, Kim JS, McGoldrick MD, Bailie GR. Respiratory distress caused by salicylism confirmed by lung biopsy. Clin Drug Invest 1999;17:79–81.
21. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325(18):1261–6.
22. The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338(8779):1345–9.
23. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321(3):129–35.
24. Rohr WD. Transitorische Myopisierung und Drucksteigerung als Medikamentennebenwirkung. [Transitory myopia and increased ocular pressure as side effects of drugs.] Fortschr Ophthalmol 1984;81(2):199–200.
25. Prince RL, Larkins RG, Alford FP. The effect of acetylsalicylic acid on plasma glucose and the response of glucose regulatory hormones to intravenous glucose and arginine in insulin treated diabetics and normal subjects. Metabolism 1981;30(3):293–8.
26. Manfredini R, Ricci L, Giganti M, La Cecilia O, Kuwornu Afi H, Chierici F, Gallerani M. An uncommon case of fluid retention simulating a congestive heart failure after aspirin consumption. Am J Med Sci 2000;320(1):72–4.
27. Necheles TF, Steinberg MH, Cameron D. Erythrocyte glutathione-peroxidase deficiency. Br J Haematol 1970;19(5):605–12.
28. Meloni T, Forteleoni G, Ogana A, Franca V. Aspirin-induced acute haemolytic anaemia in glucose-6-phosphate dehydrogenase-deficient children with systemic arthritis. Acta Haematol 1989;81(4):208–9.
29. Levy M, Heyman A. Hematological adverse effects of analgesic anti-inflammatory drugs. Hematol Rev 1990;4:177.
30. Williams JO, Mengel CE, Sullivan LW, Haq AS. Megaloblastic anemia associated with chronic ingestion of an analgesic. N Engl J Med 1969;280(6):312–13.
31. Kingham JD, Chen MC, Levy MH. Macular hemorrhage in the aging eye: the effects of anticoagulants. N Engl J Med 1988;318(17):1126–7.
32. Werblin TP, Peiffer RL. Persistent hemorrhage after extracapsular surgery associated with excessive aspirin ingestion. Am J Ophthalmol 1987;104(4):426.
33. Hanley SP, Bevan J, Cockbill SR, Heptinstall S. Differential inhibition by low-dose aspirin of human venous prostacyclin synthesis and platelet thromboxane synthesis. Lancet 1981;1(8227):969–71.

34. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978;299(2):53–9.
35. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2(8607):349–60.
36. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990;336(8719):827–30.
37. Blower AL, Brooks A, Fenn GC, Hill A, Pearce MY, Morant S, Bardhan KD. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. Aliment Pharmacol Ther 1997;11(2):283–91.
38. Piper DW, McIntosh JH, Ariotti DE, Fenton BH, MacLennan R. Analgesic ingestion and chronic peptic ulcer. Gastroenterology 1981;80(3):427–32.
39. Petroski D. Endoscopic comparison of various aspirin preparations-gastric mucosal adaptability to aspirin restudied. Curr Ther Res 1989;45:945.
40. Szabo S. Pathogenesis of gastric mucosal injury. S Afr Med J 1988;74(Suppl):35.
41. Faulkner G, Prichard P, Somerville K, Langman MJ. Aspirin and bleeding peptic ulcers in the elderly. BMJ 1988;297(6659):1311–13.
42. Freeland GR, Northington RS, Hedrich DA, Walker BR. Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. Clin Pharmacol Ther 1988;43(5):473–9.
43. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351(9118):1755–62.
44. Meade TW, Brennan PJ, Wilkes HC, Zuhrie SR. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet 1998;351(9098):233–41.
45. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Frequency of major complications of aspirin, warfarin, and intravenous heparin for secondary stroke prevention. A population-based study. Ann Intern Med 1999;130(1):14–22.
46. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, Olsen JH. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000;95(9):2218–24.
47. Tramèr MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000;85(1–2):169–82.
48. Weil J, Langman MJ, Wainwright P, Lawson DH, Rawlins M, Logan RF, Brown TP, Vessey MP, Murphy M, Colin-Jones DG. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 2000;46(1):27–31.
49. Tramèr MR. Aspirin, like all other drugs, is a poison. BMJ 2000;321(7270):1170–1.
50. Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001;52(5):563–71.
51. Bianchine JR, Procter RR, Thomas FB. Piroxicam, aspirin, and gastrointestinal blood loss. Clin Pharmacol Ther 1982;32(2):247–52.
52. Hass WK, Easton JD, Adams HP Jr, Pryse-Phillips W, Molony BA, Anderson S, Kamm B. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989;321(8):501–7.
53. Lanas A, Serrano P, Bajador E, Esteva F, Benito R, Sainz R. Evidence of aspirin use in both upper and lower gastrointestinal perforation. Gastroenterology 1997;112(3):683–9.
54. Bonavina L, DeMeester TR, McChesney L, Schwizer W, Albertucci M, Bailey RT. Drug-induced esophageal strictures. Ann Surg 1987;206(2):173–83.
55. Schreiber JB, Covington JA. Aspirin-induced esophageal hemorrhage. JAMA 1988;259(11):1647–8.
56. Barrier CH, Hirschowitz BI. Controversies in the detection and management of nonsteroidal antiinflammatory drug-induced side effects of the upper gastrointestinal tract. Arthritis Rheum 1989;32(7):926–32.
57. Suazo-Barahona J, Gallegos J, Carmona-Sanchez R, Martinez R, Robles-Diaz G. Nonsteroidal anti-inflammatory drugs and gastrocolic fistula. J Clin Gastroenterol 1998;26(4):343–5.
58. Gutnik SH, Willmott D, Ziebarth J. Gastrocolic fistula-secondary to aspirin abuse. S D J Med 1993;46(10):358–60.
59. Levine MS, Kelly MR, Laufer I, Rubesin SE, Herlinger H. Gastrocolic fistulas: the increasing role of aspirin. Radiology 1993;187(2):359–61.
60. Mielants H, Verbruggen G, Schelstraete K, Veys EM. Salicylate-induced gastrointestinal bleeding: comparison between soluble buffered, enteric-coated, and intravenous administration. J Rheumatol 1979;6(2):210–18.
61. Malfertheiner P, Stanescu A, Rogatti W, Ditschuneit H. Effects of microencapsulated vs. enteric-coated acetylsalicylic acid on gastric and duodenal mucosa: an endoscopic study. J Clin Gastroenterol 1988;10(3):269–72.
62. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch Intern Med 1996;156(14):1530–6.
63. Ward MR. Reye's syndrome: an update. Nurse Pract 1997;22(12):45–6, 49–50, 52–3.
64. Food and Drug Administration, HHS. Labeling for oral and rectal over-the-couter drug products containing aspirin and nonaspirin salicylates; Reye's Syndrome warning. Final rule. Fed Regist 2003;68(74):18861–9.
65. Zimmerman HJ. Effects of aspirin and acetaminophen on the liver. Arch Intern Med 1981;141(3 Spec No):333–42.
66. Gitlin N. Salicylate hepatotoxicity: the potential role of hypoalbuminemia. J Clin Gastroenterol 1980;2(3):281–5.
67. Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Schonberger LB. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 1999;340(18):1377–82.
68. Langford NJ. Aspirin and Reye's syndrome: is the response appropriate? J Clin Pharm Ther 2002;27(3):157–60.
69. Plotz PH, Kimberly RP. Acute effects of aspirin and acetaminophen on renal function. Arch Intern Med 1981;141(3 Spec No):343–8.
70. Delzell E, Shapiro S. A review of epidemiologic studies of nonnarcotic analgesics and chronic renal disease. Medicine (Baltimore) 1998;77(2):102–21.

71. McLaughlin JK, Lipworth L, Chow WH, Blot WJ. Analgesic use and chronic renal failure: a critical review of the epidemiologic literature. Kidney Int 1998;54(3):679–86.
72. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. JAMA 2001;286(3):315–21.
73. Fored CM, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, Lipworth L, Elinder CG, Blot WJ, McLaughlin JK, Zack MM, Nyren O. Acetaminophen, aspirin, and chronic renal failure. N Engl J Med 2001;345(25):1801–8.
74. Kanwar AJ, Belhaj MS, Bharija SC, Mohammed M. Drugs causing fixed eruptions. J Dermatol 1984;11(4):383–5.
75. Brandt KD, Palmoski MJ. Effects of salicylates and other nonsteroidal anti-inflammatory drugs on articular cartilage. Am J Med 1984;77(1A):65–9.
76. Oates JA, FitzGerald GA, Branch RA, Jackson EK, Knapp HR, Roberts LJ 2nd. Clinical implications of prostaglandin and thromboxane A2 formation (1). N Engl J Med 1988;319(11):689–98.
77. Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. Allergy 1980;35(2):149–54.
78. Farr RS, Spector SL, Wangaard CH. Evaluation of aspirin and tartrazine idiosyncrasy. J Allergy Clin Immunol 1979;64(6 pt 2):667–8.
79. Szczeklik A. The cyclooxygenase theory of aspirin-induced asthma. Eur Respir J 1990;3(5):588–93.
80. Szczeklik A. Aspirin-induced asthma: pathogenesis and clinical presentation. Allergy Proc 1992;13(4):163–73.
81. Sola Alberich R, Jammoul A, Masana L. Henoch-Schonlein purpura associated with acetylsalicylic acid. Ann Intern Med 1997;126(8):665.
82. Martelli NA. Bronchial and intravenous provocation tests with indomethacin in aspirin-sensitive asthmatics. Am Rev Respir Dis 1979;120(5):1073–9.
83. Ritter JM, Taylor GW. Fish oil in asthma. Thorax 1988;43(2):81–3.
84. Anonymous. Aspirin sensitivity in asthmatics. BMJ 1980;281(6246):958–9.
85. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. J Allergy Clin Immunol 1982;69(1 Pt 1):11–19.
86. Dubach UC, Rosner B, Pfister E. Epidemiologic study of abuse of analgesics containing phenacetin. Renal morbidity and mortality (1968-1979). N Engl J Med 1983;308(7):357–62.
87. Dubach UC, Rosner B, Sturmer T. An epidemiologic study of abuse of analgesic drugs. Effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). N Engl J Med 1991;324(3):155–60.
88. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Regular use of analgesics is a risk factor for renal cell carcinoma. Br J Cancer 1999;81(3):542–8.
89. Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Aspirin and congenital malformations. Lancet 1976;1(7974):1373–5.
90. Werler MM, Mitchell AA, Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. N Engl J Med 1989;321(24):1639–42.
91. Rumack CM, Guggenheim MA, Rumack BH, Peterson RG, Johnson ML, Braithwaite WR. Neonatal intracranial hemorrhage and maternal use of aspirin. Obstet Gynecol 1981;58(Suppl 5):S52–6.
92. Shapiro S, Siskind V, Monson RR, Heinonen OP, Kaufman DW, Slone D. Perinatal mortality and birthweight in relation to aspirin taken during pregnancy. Lancet 1976;1(7974):1375–6.
93. Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial. Lancet 1991;337(8755):1427–31.
94. Anonymous. Poisoning with enteric-coated aspirin. Lancet 1981;2(8238):130.
95. Pierce RP, Gazewood J, Blake RL Jr. Salicylate poisoning from enteric-coated aspirin. Delayed absorption may complicate management. Postgrad Med 1991;89(5):61–4.
96. Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981;141(3 Spec No):364–9.
97. Meredith TJ, Vale JA. Non-narcotic analgesics. Problems of overdosage. Drugs 1986;32(Suppl 4):177–205.
98. Dove DJ, Jones T. Delayed coma associated with salicylate intoxication. J Pediatr 1982;100(3):493–6.
99. Deykin D, Janson P, McMahon L. Ethanol potentiation of aspirin-induced prolongation of the bleeding time. N Engl J Med 1982;306(14):852–4.
100. Anonymous. Alcohol warning on over-the-counter pain medications. WHO Drug Inf 1998;12:16.
101. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A; European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143(1-2):1–13.
102. Enquete de prevention secondaire de l'infarctus du Myocarde' Research Group. A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. N Engl J Med 1982; 307(12):701–8.
103. Moore TJ, Crantz FR, Hollenberg NK, Koletsky RJ, Leboff MS, Swartz SL, Levine L, Podolsky S, Dluhy RG, Williams GH. Contribution of prostaglandins to the antihypertensive action of captopril in essential hypertension. Hypertension 1981;3(2):168–73.
104. Cowan RA, Hartnell GG, Lowdell CP, Baird IM, Leak AM. Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function. BMJ (Clin Res Ed) 1984;289(6441):347–8.
105. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. N Engl J Med 1991;324(24):1716–25.
106. McInnes GT, Brodie MJ. Drug interactions that matter. A critical reappraisal. Drugs 1988;36(1):83–110.
107. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. Chest 1998;114(Suppl 5):S511–23.
108. World Health Organization (WHO). Mechanism of action, safety and efficacy of intrauterine devices. In: Technical Report Series. Geneva: WHO, 1987;753:91.
109. Croxatto HB, Ortiz ME, Valdez E. IUD mechanisms of action. In: Bardin CW, Mishell DR, editors. Proceedings from the 4th International Conference on IUDs. Boston: Butterworth-Heinemann, 1994:44.
110. Offerhaus L. Drug interactions at excretory mechanisms. Pharmacol Ther 1981;15(1):69–78.
111. Lanas A, Bajador E, Serrano P, Arroyo M, Fuentes J, Santolaria S. Effects of nitrate and prophylactic aspirin on upper gastrointestinal bleeding: a retrospective case-control study. J Int Med Res 1998;26(3):120–8.
112. Orr JM, Abbott FS, Farrell K, Ferguson S, Sheppard I, Godolphin W. Interaction between valproic acid and aspirin in epileptic children: serum protein binding and metabolic effects. Clin Pharmacol Ther 1982;31(5):642–9.
113. Abbott FS, Kassam J, Orr JM, Farrell K. The effect of aspirin on valporic acid metabolism. Clin Pharmacol Ther 1986;40(1):94–100.

114. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Lancet 1995;346(8989):1509–14.
115. Ciccone A, Motto C, Aritzu E, Piana A, Candelise L. Negative interaction of aspirin and streptokinase in acute ischemic stroke: further analysis of the Multicenter Acute Stroke Trial—Italy. Cerebrovasc Dis 2000;10(1):61–4.
116. Akyol SM, Thompson M, Kerr DN. Renal function after prolonged consumption of aspirin. BMJ (Clin Res Ed) 1982;284(6316):631–2.
117. Harris M, Bryant LR, Danaher P, Alloway J. Effect of low dose daily aspirin on serum urate levels and urinary excretion in patients receiving probenecid for gouty arthritis. J Rheumatol 2000;27(12):2873–6.
118. Samuels MH, Pillote K, Ashex D, Nelson JC. Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. J Clin Endocrinol Metab 2003;88(12): 5710–5716.

Aciclovir

General Information

Aciclovir is an acyclic purine nucleoside. Its antiviral activity depends upon intracellular phosphorylation to its triphosphate derivative. Because of its higher affinity for viral thymidine kinase, aciclovir is phosphorylated at a much higher rate by the viral enzyme. Thus, it is almost exclusively active in infected cells, fulfilling one of the selectivity principles of antiviral drugs. In addition, aciclovir triphosphate serves as a better substrate for viral than for host cell DNA polymerase and thereby causes preferential termination of viral DNA synthesis (1).

Aciclovir is active against *Herpes simplex* virus type 1 (HSV-1), HSV-2, *Varicella zoster* virus (VZV), *Herpesvirus simiae*, and to a lesser degree Epstein–Barr virus (EBV). Resistant strains of HSV can arise owing to the emergence of thymidine kinase-deficient mutants. Other forms of resistance patterns are less common (2,3).

Aciclovir is used topically or systemically, orally or intravenously. Its therapeutic potential is most impressive in active parenchymal or systemic HSV infections. The latency stage of the viral infection is not affected. Since the blood–brain barrier is well penetrated, aciclovir is the treatment of choice for HSV encephalitis.

Very few adverse effects, generally of minor importance, have been reported (4). In immunosuppressed patients abnormal liver function, encephalopathy, and myelosuppression have been observed; however, it is unclear at present whether these adverse effects are related to the drug itself or to the underlying disorder (5–7).

Comparative studies

The effects of aciclovir and valaciclovir for anogenital herpes have been studied in HIV-infected individuals in two controlled trials (8). In the first study, 1062 patients with CD4+ counts over 100×10^6/l received valaciclovir or aciclovir for 1 year and were assessed monthly. In the second study, 467 patients were treated episodically for at least 5 days with valaciclovir or aciclovir and were assessed daily. Valaciclovir was as effective as aciclovir for suppression and episodic treatment of herpesvirus infections. Hazard ratios for the time to recurrence with valaciclovir 500 mg bd and 1000 mg od compared with aciclovir were 0.73 (95% CI = 0.50, 1.06) and 1.31 (0.94, 1.82). Valaciclovir 1000 mg bd and aciclovir had similar effects on the duration of infective episodes (HR = 0.92; CI = 0.75, 1.14). The most common adverse events, which occurred at similar rates with all regimens, were diarrhea, headache, infections, rashes, nausea, rhinitis, pharyngitis, abdominal pain, fever, depression, and cough.

Organs and Systems

Nervous system

Neurotoxicity secondary to aciclovir is rare and is associated with high plasma concentrations (SEDA-18, 299), such as result from impaired renal function (9). Although the risk is greatest with intravenous administration, neurotoxicity has previously been noted with oral use.

Symptoms of neurotoxicity, which usually appear within the first 24–72 hours of administration, include tremor, myoclonus, confusion, lethargy, agitation, hallucinations, dysarthria, asterixis, ataxia, hemiparesthesia, and seizures. While aciclovir-induced neurotoxicity is most prevalent with intravenous administration, it has also been reported after oral use in patients with terminal renal insufficiency on hemodialysis.

Neurotoxicity possibly secondary to the topical use of aciclovir has also been described (10).

- A 59-year-old woman on hemodialysis was treated with oral aciclovir 200 mg/day for ophthalmic Herpes zoster. After a few days, an ophthalmic aciclovir cream was started (one application every 6 hours) because of ipsilateral *Herpes* keratitis. After 1 week of combined oral and topical treatment, she became confused, with dysarthria and audiovisual hallucinations. Aciclovir was withdrawn and hemodialysis was initiated. Complete resolution of symptoms was achieved after three hemodialysis sessions in 3 days. Aciclovir plasma concentrations before hemodialysis were high (45 μmol/l) and fell rapidly during hemodialysis.

There is no conclusive evidence for the contribution of the topically administered aciclovir to the high plasma concentrations and subsequent neurotoxicity in this case. However, the authors argued that the existence of high aciclovir plasma concentrations, in spite of careful adjustment of the oral dosage, pointed to significant topical absorption of the drug, especially since the absorption of aciclovir through the skin and mucous membranes may be unpredictable.

Coma has been attributed to oral aciclovir (11).

- A 73-year-old man with acute respiratory failure, presumed to be secondary to amiodarone toxicity, developed sepsis and acute renal insufficiency, and required intermittent hemodialysis. Following a *Herpes simplex* labialis infection he was treated with oral aciclovir (400 mg tds). The next day he became sleepy, disoriented, and agitated. Over the next 48 hours his neurological condition deteriorated and he responded to pain

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only, had uncoordinated eye movements, tremors, facial and jaw myoclonus, increased reflexes, and hypertonia. After 7 days of aciclovir he became unresponsive and comatose. Aciclovir was withdrawn and hemodialysis carried out more frequently. His neurological status improved over a period of 4 days. Trough plasma concentrations of aciclovir were well above the upper limit of the usual target range.

This appears to be the first case of coma attributable to oral aciclovir. The fact that the patient was receiving oral rather than intravenous aciclovir and was on regular hemodialysis made neurotoxicity unlikely, and this emphasizes the need to be wary of this potentially serious complication in seriously ill elderly patients.

Sensory systems

Local application of 3% ophthalmic ointment can cause mild transient stinging. Diffuse, superficial, punctate, non-progressive keratopathy can develop. This quickly resolves after withdrawal (12,13).

Psychological, psychiatric

One report described reversible psychiatric adverse effects in three dialysis patients receiving intravenous aciclovir (8–10 mg/kg/day) (14).

Hematologic

Neutropenia and thrombocytopenia occurred in an 8-year-old boy who was treated with aciclovir 200 mg bd for 5 months for "chronic cold sores" (15). After withdrawal of aciclovir, the absolute neutrophil and platelet counts normalized within days. There was no recurrence of oral herpes lesions during the ensuing month.

Urinary tract

Renal impairment has been associated with the use of intravenous aciclovir. Transient increases in serum creatinine and urea have been observed in 14% of patients treated with bolus injections (16). These are related to crystal formation in the lower renal tubules when the solubility of aciclovir in urine is exceeded. Slow (1-hour) intravenous infusion and adequate hydration are therefore mandatory. Bolus doses are to be avoided. Dosage modifications for patients with renal insufficiency are based on creatinine clearance (4).

- Crystalluria due to aciclovir occurred within 24 hours of the start of therapy with 500 mg 8-hourly in a 4-year-old African-American boy (17). Slow intravenous infusion over 1–2 hours and volume repletion avoids the problem.

Renal toxicity has not been described in infants treated with intravenous aciclovir, 5–10 mg/kg every 8 hours for 5–10 days (18) or in children receiving aciclovir 500 mg/m^2 intravenously (19) or orally (4).

Skin

Skin reactions to aciclovir are mostly mild and transitory, including pruritus, pain, rashes, contact dermatitis, and photoallergic contact dermatitis. However, serious reactions occasionally occur (20). Antiviral drugs that have been implicated include topical aciclovir, cidofovir, idoxuridine, imiquimod, lamivudine, penciclovir, podophyllin, podophyllotoxin, trifluridine, tromantadine, vidarabine, intralesional and ophthalmic solutions of interferon, intravitreal injections of fomivirsen and foscarnet, and intraocular implants of ganciclovir. Patch-testing in these cases only rarely caused positive reactions to the antiviral drug.

A case of possible aciclovir-induced Stevens–Johnson syndrome has been reported in an HIV-positive patient with mycobacterial disease (21). However, Stevens–Johnson syndrome is associated with *Herpes simplex* infection and can be prevented by aciclovir (22).

Immunologic

Although allergy to aciclovir is unusual, it can occur; in one case it resulted in a skin rash (23).

- A 38-year-old woman of African descent, with a history of atopy and mild asthma, developed a periumbilical, erythematous, maculopapular rash and generalized pruritus after starting aciclovir. The reaction resolved within a few days after withdrawal, recurred when famciclovir was used, and again resolved when famciclovir was withdrawn. She was successfully stabilized on suppressive therapy after a graded challenge with aciclovir four times a day for 5 days.

Cross-reactivity between aciclovir and famciclovir is unusual. Aciclovir desensitization may be a novel method of treating patients with aciclovir allergy.

Contact sensitization to aciclovir is rare, but frequent application to inflamed skin in relapsing *Herpes simplex* may increase the risk of allergy. Severe contact dermatitis in a teenager has been reported.

- A 16-year-old girl with an 11-year history of frequent cold sores developed an erythematous rash and severe contact dermatitis during oral and topical aciclovir therapy (24). Patch tests showed contact sensitization to aciclovir and to the related compound ganciclovir.
- In a 44-year-old woman who used topical aciclovir for genital herpes, aciclovir contact allergy was associated with a systemic contact allergic reaction with an erythematous vesiculobullous eruption in the labial and perioral skin and a rash on the upper trunk and extremities (25). Patch tests were positive to aciclovir, valaciclovir, and ganciclovir, but not to famciclovir.

Pre-existing vesicular edematous cheilitis (probably due to contact allergy to the protecting lip salve) was aggravated after application of Zovirax cream (26). Patch tests to the lip salve were positive, but in addition there were positive photopatch tests to Zovirax cream, but not to its separate constituents.

Second-Generation Effects

Pregnancy

Animal data suggest that aciclovir is probably safe in pregnancy. There are no reports of teratogenicity in

humans, and a report of 312 pregnant women exposed to aciclovir showed no increase in the number of birth defects compared with the numbers expected in the general population (27). However, data from larger numbers of human pregnancies are not available to draw reliable conclusions about the safety of aciclovir in pregnancy.

Drug Administration

Drug administration route

Local necrosis and inflammation can occur due to extravasation of the drug at the site of injection (28).

Various local adverse effects of aciclovir eye-drops have been reported, including pruritus, burning sensations, and irritative or allergic conjunctivitis. Persistent superficial punctate keratitis, delayed epithelial healing, and epithelial dysplasia can develop (29).

References

1. Wagstaff AJ, Faulds D, Goa KL. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1994;47(1):153–205.
2. Erlich KS, Mills J, Chatis P, Mertz GJ, Busch DF, Follansbee SE, Grant RM, Crumpacker CS. Acyclovir-resistant *Herpes simplex* virus infections in patients with the acquired immunodeficiency syndrome. N Engl J Med 1989;320(5):293–6.
3. Sacks SL, Wanklin RJ, Reece DE, Hicks KA, Tyler KL, Coen DM. Progressive esophagitis from acyclovir-resistant *Herpes simplex*. Clinical roles for DNA polymerase mutants and viral heterogeneity? Ann Intern Med 1989;111(11):893–9.
4. Drucker JL, Tucker WE, Szczech M Jr. Safety studies of acyclovir: preclinical and clinical. In: Baker DA, editor. Acyclovir Therapy for Herpesvirus Infections. New York: Marcel Dekker, 1990:15.
5. Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. Ann Intern Med 1983;98(6):921–5.
6. Wade JC, Hintz M, McGuffin R, Springmeyer SC, Connor JD, Meyers JD. Treatment of cytomegalovirus pneumonia with high-dose acyclovir. Am J Med 1982;73(1A):249–56.
7. Straus SE, Smith HA, Brickman C, de Miranda P, McLaren C, Keeney RE. Acyclovir for chronic mucocutaneous *Herpes simplex* virus infection in immunosuppressed patients. Ann Intern Med 1982;96(3):270–7.
8. Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT, Crooks RJ, Acebes LO, Aiuti F, Akil B, Anderson J, Melville RL, Ballesteros Martin J, Berry A, Weiner M, Black F, Anderson PL, Bockman W, Borelli S, Bradbeer CS, Braffman M, Brandon W, Clark R, Wisniewski T, Bruun JN, Burdge D, Caputo RM, Chateauvert M, LaLonde R, Chiodo F, et al.; International Valaciclovir HSV Study Group. Valaciclovir versus aciclovir for *Herpes simplex* virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002;13(1):12–21.
9. Ernst ME, Franey RJ. Acyclovir- and ganciclovir-induced neurotoxicity. Ann Pharmacother 1998;32(1):111–13.
10. Gomez Campdera FJ, Verde E, Vozmediano MC, Valderrabano F. More about acyclovir neurotoxicity in patients on haemodialysis. Nephron 1998;78(2):228–9.
11. Rajan GR, Cobb JP, Reiss CK. Acyclovir induced coma in the intensive care unit. Anaesth Intensive Care 2000;28(3):305–7.
12. McGill J, Tormey P. Use of acyclovir in herpetic ocular infection. Am J Med 1982;73(1A):286–9.
13. Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Acyclovir. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1983;26(5):378–438.
14. Tomson CR, Goodship TH, Rodger RS. Psychiatric side-effects of acyclovir in patients with chronic renal failure. Lancet 1985;2(8451):385–6.
15. Grella M, Ofosu JR, Klein BL. Prolonged oral acyclovir administration associated with neutropenia and thrombocytopenia. Am J Emerg Med 1998;16(4):396–8.
16. Brigden D, Rosling AE, Woods NC. Renal function after acyclovir intravenous injection. Am J Med 1982; 73(1A):182–5.
17. Blossom AP, Cleary JD, Daley WP. Acyclovir-induced crystalluria. Ann Pharmacother 2002;36(3):526.
18. Yeager AS. Use of acyclovir in premature and term neonates. Am J Med 1982;73(1A):205–9.
19. Blanshard C, Benhamou Y, Dohin E, Lernestedt JO, Gazzard BG, Katlama C. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir: a randomized comparison. J Infect Dis 1995;172(3):622–8.
20. Holdiness MR. Contact dermatitis from topical antiviral drugs. Contact Dermatitis 2001;44(5):265–9.
21. Fazal BA, Turett GS, Justman JE, Hall G, Telzak EE. Stevens–Johnson syndrome induced by treatment with acyclovir. Clin Infect Dis 1995;21(4):1038–9.
22. Cheriyan S, Patterson R. Recurrent Stevens–Johnson syndrome secondary to *Herpes simplex*: a follow up on a successful management program. Allergy Asthma Proc 1996;17(2):71–3.
23. Kawsar M, Parkin JM, Forster G. Graded challenge in an aciclovir allergic patient. Sex Transm Infect 2001;77(3):204–5.
24. Wollenberg A, Baldauf C, Rueff F, Przybilla B. Allergic contact dermatitis and exanthematous drug eruption following aciclovir-cross reaction with ganciclovir. Allergo J 2000;9:96–9.
25. Lammintausta K, Makela L, Kalimo K. Rapid systemic valaciclovir reaction subsequent to aciclovir contact allergy. Contact Dermatitis 2001;45(3):181.
26. Rodriguez WJ, Bui RH, Connor JD, Kim HW, Brandt CD, Parrott RH, Burch B, Mace J. Environmental exposure of primary care personnel to ribavirin aerosol when supervising treatment of infants with respiratory syncytial virus infections. Antimicrob Agents Chemother 1987;31(7):1143–6.
27. Andrews EB, Yankaskas BC, Cordero JF, Schoeffler K, Hampp S. Acyclovir in pregnancy registry: six years' experience. The Acyclovir in Pregnancy Registry Advisory Committee. Obstet Gynecol 1992;79(1):7–13.
28. Sylvester RK, Ogden WB, Draxler CA, Lewis FB. Vesicular eruption. A local complication of concentrated acyclovir infusions. JAMA 1986;255(3):385–6.
29. Ohashi Y. Treatment of herpetic keratitis with acyclovir: benefits and problems. Ophthalmologica 1997;211(Suppl 1): 29–32.

Acipimox

General Information

Acipimox (*S*-methylpyrazine-2-carboxylic acid 4-oxide) is structurally related to nicotinic acid. There were flushing and gastrointestinal disturbances in 7137 patients, of whom 15% stopped taking the drug because of adverse effects; there were no adverse effects on blood glucose or uric acid (1). Of 32 patients with hypertriglyceridemia, excessive hypertriglyceridemia, and combined hyperlipidemia, acipimox had to be withdrawn in 10 cases, because of adverse effects or absence of clinical response (2). The other 22 completed 6 months of treatment with no adverse effects. The authors claimed that acipimox is much better tolerated than nicotinic acid; it has fewer adverse effects and can therefore be used as a second-line drug.

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In an open study, blood glucose was on average slightly lowered in 3009 type II diabetics given acipimox for at least 2 months (3).

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Acivicin

See also Cytostatic and immunosuppressant drugs

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Besides myelotoxicity, acivicin is neurotoxic, and can cause lethargy and auditory and visual hallucinations. Some patients have nystagmus, incontinence, and severe depression (1,2).

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Acoraceae

See also Herbal medicines

General Information

Acorus calamus was originally classified as a member of the arum family (Araceae), but is now designated as belonging to its own family, the Acoraceae, of which it is the only member.

Acorus calamus

Acorus calamus (calamus root, sweet flag, rat root, sweet sedge, flag root, sweet calomel, sweet myrtle, sweet cane, sweet rush, beewort, muskrat root, pine root) contains several active constituents called "asarones." The basic structure is 2,4,5-trimethoxy-1-propenylbenzene, which is related to the hallucinogen 3,4-methylenedioxyphenylisopropylamine (MDA). The amounts of the asarones in calamus rhizomes vary considerably with the botanical variety. For example, there are high concentrations in triploid calamus from Eastern Europe but none detectable in the diploid North American variety.

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Acorus calamus has in vitro antiproliferative and immunosuppressive actions (1).

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Acrisorcin

See also Disinfectants and antiseptics

General Information

Acrisorcin (aminoacridine 4-hexylresorcinolate) has been used for induction of abortion in mid-trimester pregnancies. Abortion was produced when a 0.1% solution of acrisorcin was introduced into the extra-amniotic space in 23 women. All patients aborted after a mean induction-delivery interval of 59 hours (SEDA-11, 474) (1).

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Acrivastine

See also Antihistamines

General Information

Acrivastine is a second-generation antihistamine that has not been the subject of recent studies; earlier work was insufficient to substantiate statements that it was non-sedating.

Organs and Systems

Nervous system

Five of thirty-five patients taking acrivastine reported drowsiness compared with none in the placebo group (SEDA-14, 135). In another study acrivastine 8 mg did not impair nervous system function (SEDA-21, 172). The usual dose is 8 mg tds, which is effective in treating seasonal allergic rhinitis and has been stated to be without sedative effects (1). However, acrivastine does have a small but significant additive effect with alcohol at a dose of 8 mg (2).

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Acrylic bone cement

General Information

Local biocompatibility

Although polymerized polymethylmethacrylate is a biocompatible material, it is not biocompatible during the brief time it takes to set, during which it releases 130 calories/gram and can cause a rise in temperature up to 120°C. This temperature rise can be reduced by various techniques, although the thermal tolerance of the tissues affected is low (56°C and 72°C for coagulation of body proteins and bone collagen respectively). This is the main factor that is responsible for bone necrosis associated with acrylic bone cement. To avoid this, sucrose crystals have been added to acrylic cement. The mixture has a lower polymerization temperature and greater porosity, allowing for better ingrowth of bone into the cement pores (1); however, the resultant lower mechanical resistance limits its use (2,3). The same can be achieved by adding tricalcium phosphate, which lowers the reaction temperature. The non-polymerized monomer is cytotoxic (4), which can cause histopathological changes in soft tissues and bones.

Regional damage

Regional damage from methylmethacrylate is generally the result of poor surgical technique, whereby the cement inadvertently reaches other tissues and structures. For example, leaking methylmethacrylate cement during fixation of the acetabular cup in a total hip replacement can cause sciatic nerve compression and result in severe lasting leg pain (5).

Organs and Systems

Cardiovascular

Cardiovascular reactions to acrylic bone cement are a common complication in bone surgery. It is believed that cementation activates an adrenocortical response, increasing the blood pressure during general anesthesia (6,7); during spinal anesthesia this response is suppressed and the blood pressure falls. The mechanism is thought to be by a direct effect on the blood pressure through the kallikrein–kinin system, since aprotinin (Trasylol), an inhibitor of kallikrein, prevents the fall in arterial pressure if it is given during the application of acrylic bone cement (8).

Some investigators suggested that implantation of acrylic bone cement into the femur increases plasma histamine, which, especially in elderly patients with pre-existing cardiac diseases and/or hypovolemia, can cause serious, sometimes fatal, cardiovascular complications (9).

Respiratory

Since adverse effects in humans develop within 2–5 minutes of fixation, with features of pulmonary insufficiency, direct pulmonary damage has been

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Although polymerized polymethylmethacrylate is a biocompatible material, it is not biocompatible during the brief time it takes to set, during which it releases 130 calories/gram and can cause a rise in temperature up to 120°C. This temperature rise can be reduced by various techniques, although the thermal tolerance of the tissues affected is low (56°C and 72°C for coagulation of body proteins and bone collagen respectively). This is the main factor that is responsible for bone necrosis associated with acrylic bone cement. To avoid this, sucrose crystals have been added to acrylic cement. The mixture has a lower polymerization temperature and greater porosity, allowing for better ingrowth of bone into the cement pores (1); however, the resultant lower mechanical resistance limits its use (2,3). The same can be achieved by adding tricalcium phosphate, which lowers the reaction temperature. The non-polymerized monomer is cytotoxic (4), which can cause histopathological changes in soft tissues and bones.

Regional damage

Regional damage from methylmethacrylate is generally the result of poor surgical technique, whereby the cement inadvertently reaches other tissues and structures. For example, leaking methylmethacrylate cement during fixation of the acetabular cup in a total hip replacement can cause sciatic nerve compression and result in severe lasting leg pain (5).

Organs and Systems

Cardiovascular

Cardiovascular reactions to acrylic bone cement are a common complication in bone surgery. It is believed that cementation activates an adrenocortical response, increasing the blood pressure during general anesthesia (6,7); during spinal anesthesia this response is suppressed and the blood pressure falls. The mechanism is thought to be by a direct effect on the blood pressure through the kallikrein–kinin system, since aprotinin (Trasylol), an inhibitor of kallikrein, prevents the fall in arterial pressure if it is given during the application of acrylic bone cement (8).

Some investigators suggested that implantation of acrylic bone cement into the femur increases plasma histamine, which, especially in elderly patients with pre-existing cardiac diseases and/or hypovolemia, can cause serious, sometimes fatal, cardiovascular complications (9).

Respiratory

Since adverse effects in humans develop within 2–5 minutes of fixation, with features of pulmonary insufficiency, direct pulmonary damage has been

postulated, with the cardiovascular effects being a consequence of hypoxemia (10–12). This has been demonstrated by lactase dehydrogenase isomer determinations, fractions 3 and 4 being significantly raised. These isozymes are released as a result of pulmonary mitochondrial injury caused by hypoxia. Methylmethacrylate monomer vapour can irritate the respiratory tract, eyes, and skin.

Immunologic

Methylmethacrylate is essentially an immunologically inert implant material, but it induces an inflammatory mononuclear cell migration (13,14). Both cemented and cementless prostheses cause a foreign-body-type host response. A new connective tissue capsule is formed around the artificial joint, which is coarser than normal. The reaction is partly granulomatous, with a tendency to necrosis and loosening of the prosthesis. After an initial necrotic phase of 2–3 weeks repair follows, leading to stabilization within 2 years.

Sensitization can occur in patients, surgeons, and dentists and is occasionally reported (15). As most surgical gloves do not provide a reliable barrier, additional gloves are recommended. Contact dermatitis, dizziness, and nausea and vomiting occur. Ethylene oxide present in acrylic bone cement can cause acute allergic reactions in sensitized patients (16).

Infection risk

Addition of materials (for example antimicrobial drugs or radio-opaque contrast materials) to acrylic bone cement can cause mechanical weakness due to loss of homogeneity and greater water resorption. Antimicrobial drugs have been added to combat the problem of microbial adherence. However, this can lead to a considerable dead biofilm mass on the polymethylmethacrylate surface, promoting late infections by providing a surface attractive to other strains of bacteria (17).

References

1. Rijke AM, Rieger MR, McLaughlin RE, McCoy S. Porous acrylic cement. J Biomed Mater Res 1977;11(3):373–94.
2. Feith R. Arcrylic cement. Ned Tijdschr Geneeskd 1978;122:64.
3. Rijke AM. Bijwerkingen van methylmethacrylaat-botcement. [Side effects of methylmethacrylate bone cement.] Ned Tijdschr Geneeskd 1980;124(6):180–3.
4. Fediukovich LV, Egorova AB. Genotoksicheskii effekt akrilatov. [Genotoxic effect of acrylates.] Gig Sanit 1991;(12):62–4.
5. Oleksak M, Edge AJ. Compression of the sciatic nerve by methylmethacrylate cement after total hip replacement. J Bone Joint Surg Br 1992;74(5):729–30.
6. Svartling N, Lehtinen AM, Tarkkanen L. The effect of anaesthesia on changes in blood pressure and plasma cortisol levels induced by cementation with methylmethacrylate. Acta Anaesthesiol Scand 1986;30(3):247–52.
7. Esemenli BT, Toker K, Lawrence R. Hypotension associated with methylmethacrylate in partial hip arthroplasties. The role of femoral canal size. Orthop Rev 1991;20(7):619–23.
8. Arac SS, Ercan ZS, Turker RK. Prevention by aprotinin of the hypotension due to acrylic cement implantation into the bone. Curr Ther Res 1980;28:554.
9. Tryba M, Linde I, Voshage G, Zenz M. Histaminfreisetzung und kardiovaskulare Reaktionen nach Implantation von Knochenzement bei totalem Huftgelenkersatz. [Histamine release and cardiovascular reactions to implantation of bone cement during total hip replacement.] Anaesthesist 1991;40(1):25–32.
10. Saint-Maurice C, Migne J, Maurin JP, Vedrine Y, Raud J, Lamas JP. Accidents consécutifs au scellement des prothéses articulaires. [Complications following cementing of joint prosthesis.] Ann Anesthesiol Fr 1977;18(7-8):647–54.
11. Shirai K. [Untoward effect of monomeric methylmethacrylate cement on the respiratory system during surgery.] Masui 1975;24(9):886–90.
12. Pickering CA, Bainbridge D, Birtwistle IH, Griffiths DL. Occupational asthma due to methyl methacrylate in an orthopaedic theatre sister. BMJ (Clin Res Ed) 1986;292(6532):1362–3.
13. Santavirta S, Konttinen YT, Bergroth V, Gronblad M. Lack of immune response to methyl methacrylate in lymphocyte cultures. Acta Orthop Scand 1991;62(1):29–32.
14. Santavirta S, Gristina A, Konttinen YT. Cemented versus cementless hip arthroplasty. A review of prosthetic biocompatibility. Acta Orthop Scand 1992;63(2):225–32.
15. Donaghy M, Rushworth G, Jacobs JM. Generalized peripheral neuropathy in a dental technician exposed to methyl methacrylate monomer. Neurology 1991;41(7):1112–16.
16. Rumpf KW, Rieger J, Jansen J, Scherer M, Seubert S, Seubert A, Sellin HJ. Quincke's edema in a dialysis patient after administration of acrylic bone cement: possible role of ethylene oxide allergy. Arch Orthop Trauma Surg 1986;105(4):250–2.
17. Chang CC, Merritt K. Microbial adherence on poly(methyl methacrylate) (PMMA) surfaces. J Biomed Mater Res 1992;26(2):197–207.

Activated charcoal

General Information

Activated charcoal is a standard therapy for gut decontamination after self-poisoning. It has two uses. If given within an hour or two after acute self-poisoning it can adsorb the drug and prevent it from being absorbed; in this case a single dose of activated charcoal 50 g is sufficient. However, some drugs are secreted into the gut after absorption and can be adsorbed by charcoal, preventing re-absorption; in this case repeated doses of activated charcoal 50 g 6-hourly can be used.

In a randomized study in 401 patients who had taken an overdose of oleander seeds, which contain cardiac glycosides, activated charcoal 50 g every 6 hours for 3 days was compared with sterile water. There were fewer deaths in the treatment group, 2.5% versus 8% (1). There were no important adverse effects.

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Organs and Systems

Respiratory

Pulmonary aspiration is an ever-present risk of using charcoal, especially in semi-conscious patients (2). Povidone, which is used as a suspending agent of charcoal, can cause pneumonitis, which can lead to respiratory failure and death.

Electrolyte balance

Hyponatremic dehydration has been described when charcoal was combined with sorbitol to treat theophylline overdose in a child (SED-12, 951) (3).

Gastrointestinal

- Esophageal laceration with charcoal mediastinum has been reported in a 19-year-old woman who underwent multiple attempts at orogastric lavage with isotonic saline followed by 50 g of activated charcoal and sorbitol via the orogastric tube for a drug overdose (4). She recovered after surgical intervention.

Two formulations of activated charcoal 50 g (Carbomix, made into a slurry with 400 ml of tap water, and Actidose-Aqua, which came as a 240 ml suspension) have been compared in a prospective, randomized, single-blind study in 97 patients (5). The mean total dose of Carbomix (26.5 g) was significantly higher than the mean total dose of Actidose-Aqua (19.5 g); the reasons for this difference were not stated. The rates of vomiting did not differ between patients who received Carbomix (6%) or Actidose-Aqua (8%), and were low compared with previous reports (13%).

Though usually innocuous, activated charcoal can in large or multiple doses, such as may be needed in severe poisoning, cause intestinal obstruction (3,6). Pseudo-obstruction can also occur if drugs that inhibit intestinal motility are given at the same time, and sometimes it is not clear which process has occurred (SED-12, 951) (SEDA-17, 426) (6).

References

1. de Silva HA, Fonseka MM, Pathmeswaran A, Alahakone DG, Ratnatilake GA, Gunatilake SB, Ranasinha CD, Lalloo DG, Aronson JK, de Silva HJ. Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. Lancet 2003;361(9373):1935–8.
2. Menzies DG, Busuttil A, Prescott LF. Fatal pulmonary aspiration of oral activated charcoal. BMJ 1988;297(6646): 459–60.
3. Watson WA, Cremer KF, Chapman JA. Gastrointestinal obstruction associated with multiple-dose activated charcoal. J Emerg Med 1986;4(5):401–7.
4. Caravati EM, Knight HH, Linscott MS Jr, Stringham JC. Esophageal laceration and charcoal mediastinum complicating gastric lavage. J Emerg Med 2001;20(3):273–6.
5. Boyd R, Hanson J. Prospective single blinded randomised controlled trial of two orally administered activated charcoal preparations. J Accid Emerg Med 1999;16(1):24–5.
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Adefovir

General Information

Adefovir is an adenine analogue reverse transcriptase inhibitor. While it has activity against both HIV and hepatitis B, its use in HIV infection is limited by nephrotoxicity due to the high doses needed (1). The dose used for treatment of hepatitis B is about one-tenth that needed to treat HIV infection, so patients with hepatitis B must have co-infection with HIV ruled out before treatment is started.

Organs and Systems

Liver

In 35 patients co-infected with hepatitis B virus and HIV given adefovir 10 mg/day plus lamivudine 150 mg bd as part of treatment for hepatitis B and followed for 48 weeks, common adverse effects included raised transaminases, particularly alanine transaminase, increased serum creatinine, and increased blood glucose (2). Concerns about the study include the small number of patients and the lack of a comparison group.

Urinary tract

Adefovir is nephrotoxic, particularly at high doses, and the possible mechanism has been investigated in a 39-year-old man, who had severe acute tubular degenerative changes mainly affecting the proximal tubule; the mitochondria were significantly enlarged, possibly as a result of depletion of mitochondrial DNA (3).

References

1. Danta M, Dusheiko G. Adefovir dipivoxil: review of a novel acyclic nucleoside analogue. Int J Clin Pract 2004;58(9): 877–86.
2. Benhamou Y, Bochet M, Thibault V, Calvez V, Fievet MH, Vig P, Gibbs CS, Brosgart C, Fry J, Namini H, Katlama C, Poynard T. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. Lancet 2001;358(9283):718–23.
3. Tanji N, Tanji K, Kambham N, Markowitz GS, Bell A, D'agati VD. Adefovir nephrotoxicity: possible role of mitochondrial DNA depletion. Hum Pathol 2001;32(7):734–40.

Ademetionine

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Ademetionine (*S*-adenosylmethionine) has anti-inflammatory and analgesic effects in animals. Convincing evidence of these effects in man is still lacking. In trials in osteoarthritis, as presented at a symposium organized by the manufacturers (and thus open to selection bias), ademetionine was well tolerated

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(1). In a large, uncontrolled, short-term Phase IV trial, adverse effects (moderate or severe) were reported by 21% of the patients, with withdrawal in 5.2%. Adverse effects were mainly gastrointestinal (nausea, stomachache, heartburn, diarrhea), CNS symptoms (headache, dizziness, sleep disturbances, fatigue), and skin rashes.

Reference

1. di Padova C. S-adenosylmethionine in the treatment of osteoarthritis. Review of the clinical studies. Am J Med 1987;83(5A):60–5.

Adenosine and adenosine triphosphate (ATP)

See also Antidysrhythmic drugs

General Information

Adenosine and adenosine triphosphate (ATP), its phosphorylated derivative, have been used to treat acute paroxysmal supraventricular tachycardias and adenosine has also been used in the diagnosis of narrow-and broad-complex tachycardias (SEDA-16, 176).

Several reviews of the clinical pharmacology, actions, therapeutic uses, and adverse reactions and interactions of adenosine and ATP have appeared (1–4). After intravenous administration adenosine enters cells, disappearing from the blood with a half-life of less than 10 seconds; intracellularly it is phosphorylated to cyclic AMP. Its mechanism of action as an antidysrhythmic drug is not known, but it may act by an effect at adenosine receptors on the cell membrane. Its electrophysiological effects are to prolong AV nodal conduction time by prolonging the AH interval, without an effect on the HV interval. The pharmacological and adverse effects of adenosine triphosphate are similar to those of adenosine.

Although adenosine and ATP very commonly cause adverse effects, they are generally mild and usually transient, because adenosine is rapidly eliminated from the blood (with a half-life of less than 10 seconds). Adverse effects have been reported in 81% of patients given adenosine and 94% of patients given ATP (5). Exercise reduces the non-cardiac adverse effects and the incidence of major dysrhythmias (6). Reducing the duration of adenosine infusion from 6 to 4 minutes reduced the incidence of chest discomfort and ischemic ST segment changes, but had no impact on non-cardiac effects (7).

Several studies have reported the efficacy and safety of adenosine and ATP in the treatment of tachycardias in children (8–11).

In 18 children with aortic valve disease or Kawasaki disease, adenosine stress myocardial perfusion imaging was associated with the usual adverse effects, most commonly flushing and dyspnea (12).

Exercise reduces both non-cardiac adverse effects and dysrhythmias in patients who are given adenosine for diagnostic purposes in myocardial perfusion imaging (SEDA-21, 197). This has been confirmed in two studies. In the first of these, 793 patients were given an intravenous infusion of adenosine 140 micrograms/kg/minute while exercising for 6 minutes or for a similar time without exercise (13). The rate of hypotension and dysrhythmias was significantly less in those who exercised (14 of 507) than in those who did not exercise (16 of 286). Overall reactions were more common in women than in men (5.7 versus 1.8%). All the adverse effects were transient and no specific therapy was required. The authors attributed the difference to the increase in sympathetic tone during exercise, which would have partly counteracted the hypotension and the negative chronotropic and negative dromotropic effects of adenosine. However, there was a major difference between the two groups, in that those who did not take exercise were considered unfit for exercise, which may have been associated with an increased risk of adverse effects. Nevertheless, the authors discarded that possibility, because the frequency of adverse reactions in those who did not take exercise was similar to frequencies that have previously been reported.

In the second study 19 patients received an intravenous infusion of adenosine 140 micrograms/kg/minute for 4 minutes during exercise or for 6 minutes without exercise; the patients undertook both protocols (14). Again, there were fewer adverse effects in those who took exercise, but only hypotension, chest pain, and headache were significantly different; there was a reduction in the frequency of flushing, which was almost significant. In addition, adverse effects were experienced for longer and the severity was greater in those who did not take exercise.

Organs and Systems

Cardiovascular

The most common cardiac effects are atrioventricular block, sinus bradycardia, and ventricular extra beats. Occasionally serious dysrhythmias occur (SEDA-17, 219), including ventricular fibrillation (15). ATP can cause transient atrial fibrillation (16). Chest pain occurs in 30–50% of patients and dyspnea and chest discomfort in 35–55%. Chest pain can occur in patients with and without coronary artery disease, and the symptoms are not always typical of cardiac pain.

Myocardial ischemia

Adenosine can cause cardiac ischemia by activating adenosine A1 receptors in the heart. However, in a double-blind, placebo-controlled, crossover study in eight healthy volunteers, adenosine 100 μg/kg/minute did not alter ischemic pain in an exercising arm (17). Otherwise, the usual adverse effects were noted, including facial flushing and mild chest tightness.

Hypotension

When adenosine (70 micrograms/kg/minute) was given by intravenous infusion to 45 patients with acute myocardial infarction preceding balloon angioplasty, one patient developed persisting hypotension in conjunction with a large inferolateral myocardial infarction (18). Transient hypotension in three other patients resolved with a reduction in dosage. There were no cases of atrioventricular block.

(1). In a large, uncontrolled, short-term Phase IV trial, adverse effects (moderate or severe) were reported by 21% of the patients, with withdrawal in 5.2%. Adverse effects were mainly gastrointestinal (nausea, stomachache, heartburn, diarrhea), CNS symptoms (headache, dizziness, sleep disturbances, fatigue), and skin rashes.

Reference

1. di Padova C. S-adenosylmethionine in the treatment of osteoarthritis. Review of the clinical studies. Am J Med 1987;83(5A):60–5.

Adenosine and adenosine triphosphate (ATP)

See also Antidysrhythmic drugs

General Information

Adenosine and adenosine triphosphate (ATP), its phosphorylated derivative, have been used to treat acute paroxysmal supraventricular tachycardias and adenosine has also been used in the diagnosis of narrow-and broad-complex tachycardias (SEDA-16, 176).

Several reviews of the clinical pharmacology, actions, therapeutic uses, and adverse reactions and interactions of adenosine and ATP have appeared (1–4). After intravenous administration adenosine enters cells, disappearing from the blood with a half-life of less than 10 seconds; intracellularly it is phosphorylated to cyclic AMP. Its mechanism of action as an antidysrhythmic drug is not known, but it may act by an effect at adenosine receptors on the cell membrane. Its electrophysiological effects are to prolong AV nodal conduction time by prolonging the AH interval, without an effect on the HV interval. The pharmacological and adverse effects of adenosine triphosphate are similar to those of adenosine.

Although adenosine and ATP very commonly cause adverse effects, they are generally mild and usually transient, because adenosine is rapidly eliminated from the blood (with a half-life of less than 10 seconds). Adverse effects have been reported in 81% of patients given adenosine and 94% of patients given ATP (5). Exercise reduces the non-cardiac adverse effects and the incidence of major dysrhythmias (6). Reducing the duration of adenosine infusion from 6 to 4 minutes reduced the incidence of chest discomfort and ischemic ST segment changes, but had no impact on non-cardiac effects (7).

Several studies have reported the efficacy and safety of adenosine and ATP in the treatment of tachycardias in children (8–11).

In 18 children with aortic valve disease or Kawasaki disease, adenosine stress myocardial perfusion imaging was associated with the usual adverse effects, most commonly flushing and dyspnea (12).

Exercise reduces both non-cardiac adverse effects and dysrhythmias in patients who are given adenosine for diagnostic purposes in myocardial perfusion imaging (SEDA-21, 197). This has been confirmed in two studies. In the first of these, 793 patients were given an intravenous infusion of adenosine 140 micrograms/kg/minute while exercising for 6 minutes or for a similar time without exercise (13). The rate of hypotension and dysrhythmias was significantly less in those who exercised (14 of 507) than in those who did not exercise (16 of 286). Overall reactions were more common in women than in men (5.7 versus 1.8%). All the adverse effects were transient and no specific therapy was required. The authors attributed the difference to the increase in sympathetic tone during exercise, which would have partly counteracted the hypotension and the negative chronotropic and negative dromotropic effects of adenosine. However, there was a major difference between the two groups, in that those who did not take exercise were considered unfit for exercise, which may have been associated with an increased risk of adverse effects. Nevertheless, the authors discarded that possibility, because the frequency of adverse reactions in those who did not take exercise was similar to frequencies that have previously been reported.

In the second study 19 patients received an intravenous infusion of adenosine 140 micrograms/kg/minute for 4 minutes during exercise or for 6 minutes without exercise; the patients undertook both protocols (14). Again, there were fewer adverse effects in those who took exercise, but only hypotension, chest pain, and headache were significantly different; there was a reduction in the frequency of flushing, which was almost significant. In addition, adverse effects were experienced for longer and the severity was greater in those who did not take exercise.

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Symptomatic hypotension has occasionally been reported in patients with myocardial infarction who have been given adenosine (SEDA-20, 174).

An infusion of adenosine, 25 micrograms/kg, in 15 women undergoing anesthesia for major gynecological procedures was effective in maintaining hemodynamic stability during operation in addition to conventional anesthesia (19). It caused a significantly greater fall in systolic blood pressure and increase in heart rate than remifentanil in a comparable group. In four cases ephedrine was required for hypotension that was refractory to intravenous fluids or a temporary reduction in the infusion rate of adenosine. Two patients also required atropine for prolonged bradycardia.

Cardiac dysrhythmias

In patients with ischemic heart disease adenosine can prolong the QT_c interval and can increase the frequency of ventricular extra beats when there is myocardial scarring. It also causes increased release of catecholamines, and this may be the mechanism whereby it causes dysrhythmias in susceptible patients. If a dysrhythmia occurs, theophylline or one of its derivatives may be beneficial (20).

Of 100 patients who received intravenous adenosine in hospital (mean dose 7.8 mg) two had a dysrhythmia other than that for which they were being treated (21).

- A 53-year-old man with a dilated cardiomyopathy was given adenosine 6 mg for a regular broad-complex tachycardia; the dysrhythmia resolved but was followed by prolonged asystole and cyanosis for about 15 seconds.
- A 64-year-old woman with atrial fibrillation was given adenosine 12 mg; she developed a non-sustained polymorphous ventricular tachycardia followed by sustained ventricular fibrillation requiring DC shock.

In the whole series, about 40% of the patients received adenosine unnecessarily, having atrial fibrillation or atrial flutter, and the authors suggested that misuse of this sort resulted in unnecessary expense and increased risks of adverse effects. Most of this misuse was attributed to misdiagnosis by house officers who thought that rapid atrial fibrillation was a paroxysmal supraventricular tachycardia. Very few thought that adenosine would be likely to terminate atrial fibrillation.

Adenosine is contraindicated in patients with aberrant conduction pathways, because it can cause cardiac dysrhythmias. Supraventricular dysrhythmias occurred in three children with Wolff–Parkinson–White syndrome who were given intravenous adenosine (22).

There have been reports of cardiac dysrhythmias in patients given either an intravenous infusion of adenosine or a single bolus dose.

- A 38-year-old man was given intravenous adenosine 6 mg for a narrow-complex tachycardia (20). Within about 1 minute his heart rate fell from 230/minute to bradycardia and then asystole. Cardiopulmonary resuscitation was ineffective. At autopsy there was a 75% occlusion of one of the coronary arteries (unspecified).

The cause of the dysrhythmia in response to adenosine was not clear. He was not known to be taking other drugs (for example dipyridamole) that might have potentiated the action of adenosine.

- A 56-year-old man was given adenosine 12 mg for a narrow-complex tachycardia on four occasions, and on each occasion developed transient atrial fibrillation for a few minutes thereafter. He had a concealed left-sided accessory pathway, which was successfully ablated (23).
- An 86-year-old woman was given adenosine 12 mg intravenously for sustained supraventricular tachycardia, which terminated but was followed by atrial fibrillation and paroxysmal ventricular tachycardia (24). Cardioversion was unsuccessful, but normal sinus rhythm was obtained with procainamide. This followed an anteroseptal myocardial infarction.
- A 75-year-old man who had had coronary bypass surgery was given an intravenous infusion of adenosine for stress testing (25). After 1 minute he developed a three-beat run of wide-complex tachycardia, followed by a 20-second run of a regular wide-complex tachycardia at a rate of 115/minute. There was left bundle branch block, and the tachycardia ended spontaneously. Adenosine infusion was continued and some ventricular extra beats with the same configuration occurred. In this case there was impaired perfusion of the left ventricle.
- In a 60-year-old woman with atrial flutter with 2:1 block and a ventricular rate of 130/minute, the ventricular rate increased paradoxically to 260/minute with 1:1 conduction after intravenous administration of adenosine 6 mg; it responded to intravenous amiodarone 300 mg (26).
- A 52-year-old woman with a wide-complex tachycardia was given adenosine 6, 12, and another 12 mg as intravenous bolus doses; immediately after the third dose she developed ventricular fibrillation (27). She recovered with cardioversion.

In the last case the authors did not discuss the possibility that the presence of digoxin (serum concentration 1.8 ng/ml) may have contributed; the risk of cardiac dysrhythmias after electrical cardioversion is increased in the presence of digoxin (SEDA-8, 174), and the same might be true of chemical cardioversion.

In a prospective study of 187 episodes of tachycardia in 127 unselected patients adenosine was given in an average dose of 9.7 mg (28). In 108 cases, adenosine induced transient ventricular extra beats or non-sustained ventricular tachycardia after successful termination of supraventricular tachycardia; more than half had a right bundle branch block morphology that suggested that the dysrhythmias had originated from the inferior left ventricular septum.

Heart block

The frequency of atrioventricular block has been studied in 600 patients who underwent stress testing with intravenous adenosine 140 micrograms/kg/minute for 6 minutes (29). The patients were young (under 49 years old; $n = 75$), middle-aged (50–65 years; $n = 214$), old (66–75 years; $n = 195$), or very old (over 75 years; $n = 116$). The respective frequencies of first-degree atrioventricular block were 15, 9.3, 14, and 17% (overall

Table 1 The incidence of atrioventricular block with adenosine

Type of block	Baseline PR interval over 200 ms ($n = 43$)	Baseline PR interval under 200 ms ($n = 557$)
Further prolongation of PR interval	49%	10%
Second-degree block	37%	8%
Third-degree block	14%	1%

average 13%), of second-degree block 15, 7.0, 8.7, and 16% (overall average 10%), and of third-degree block 2.7, 2.3, 1.0, and 2.6% (overall average 2.0%). The differences with age were not statistically significant. All types of atrioventricular block were of short duration, were well tolerated, and did not require withdrawal of adenosine or specific treatment.

In four out of nine patients with heart transplants second-degree or third-degree atrioventricular block occurred during the administration of adenosine 140 micrograms/kg/minute over 6 minutes (30). In two patients the infusion had to be interrupted because of severe discomfort and chest pain.

The incidence of atrioventricular block has been reported in 600 consecutive patients who underwent stress myocardial perfusion imaging with adenosine (140 micrograms/kg/minute for 6 minutes), and of whom 43 had first-degree heart block before adenosine and 557 had a baseline PR interval less than 200 ms (Table 1) (31). The heart block in all cases was of short duration, was not associated with any specific symptoms, and in no case required specific treatment. The risk of atrioventricular block during adenosine infusion was not increased by the presence of other drugs that might have caused atrioventricular block (digitalis, beta-blockers, diltiazem, verapamil).

Respiratory

Adenosine can cause bronchoconstriction with asthma (32), and a history of bronchoconstriction is a contraindication to intravenous adenosine.

In 94 patients with chronic obstructive pulmonary disease who were given adenosine in an initial dosage of 50 micrograms/kg/minute, increasing to 140 micrograms/kg/minute if adverse effects did not occur, there was only a slight and insignificant fall in FEV_1 at the highest dose of adenosine (33). However, four patients had a fall in FEV_1 of 20% or more, although without shortness of breath or evidence of bronchospasm; in these the dosage of adenosine was reduced to 100 micrograms/kg/minute. Two other patients had shortness of breath with no fall in FEV_1 or bronchospasm, and the dosage was reduced to 100 micrograms/kg/minute. There was no difference in the fall in FEV_1 between patients who had a history of asthma and those who did not. Other adverse effects included light-headedness ($n = 26$), dyspnea ($n = 17$), headache ($n = 14$), flushing ($n = 8$), hypotension ($n = 7$), chest pain ($n = 6$), and nausea ($n = 2$). In a subsequent study in 117 patients, two had symptomatic bronchospasm during adenosine infusion. In two other patients in whom bronchospasm was present before treatment, bronchospasm did not develop when adenosine was infused at the highest dosage.

In another study, 63 of 122 patients had breathlessness during cardiac stress testing with adenosine but none had associated bronchospasm (34). Pre-test lung function did not predict the risk of breathlessness and neither chronic obstructive airways disease nor smoking increased the risk. The authors concluded that breathlessness during adenosine stress testing is not due to bronchospasm.

Nervous system

Adenosine has been used intrathecally to treat pain, but can itself cause backache (SEDA-23, 197) (35). In a placebo-controlled study in 40 healthy volunteers, who were given intrathecal adenosine 2 mg in 2 ml of saline, 13 had a mild headache, nine had mild to moderate backache, and one had mild aching in the thigh, compared with none of those who were given saline alone (36). No headaches or leg aches occurred later than 6 hours after the injection, but the backaches occurred at 6–24 hours; there were no later symptoms.

In a randomized, double-blind study of two doses of intrathecal adenosine in 35 volunteers with experimental hypersensitivity induced by capsaicin, intrathecal adenosine 0.5 or 2 mg in 2 ml of saline, but not saline alone, equally reduced areas of allodynia and hyperalgesia from capsaicin (37). There were adverse effects in 1, 2, and 6 of the volunteers who received saline, 0.5 mg, and 2.0 mg of adenosine respectively. The adverse effects were headache, backache, and leg or groin ache. Intravenous aminophylline 5 mg/kg, given 2 hours after the adenosine, did not reverse the effects of adenosine.

Of 12 healthy volunteers given an intrathecal injection of adenosine (500–2000 micrograms) one volunteer had transient lumbar pain lasting 30 minutes after an injection of 2000 micrograms (38). There were no adverse effects at lower doses.

Adenosine can cause increased intracranial pressure (39).

Gastrointestinal

Adenosine can cause transient epigastric pain mimicking that of peptic ulceration (40).

Immunologic

- An anaphylactic reaction has been reported in a 75-year-old woman who was given adenosine 12 mg for a supraventricular tachycardia. She developed bronchospasm and profound inspiratory stridor, her arterial blood pressure fell to 50/30 mmHg from an arterial systolic pressure of 70 mmHg, and she recovered with appropriate treatment (41).

Death

Two cases of sudden death have been reported soon after the administration of adenosine for presumed supraventricular tachycardia, which turned out to be atrial fibrillation (42). The authors thought that both patients may have been unable to cope with the sudden momentary loss of cardiac function that would have occurred

immediately after the administration of adenosine; in one case, a patient with chronic lung disease, bronchospasm may have contributed.

Drug Administration

Drug administration route

The standard regimen for stress testing with intravenous adenosine is 140 micrograms/kg/minute for 6 minutes. However, in 599 patients a 3-minute infusion was associated with a lower frequency of some adverse effects (specifically flushing, headache, neck pain, and atrioventricular block) and had similar sensitivity in the diagnosis of coronary artery disease (43).

Intracoronary adenosine has been compared with intravenous adenosine for the measure of fractional flow reserve in 52 patients with coronary artery lesions (44). The intravenous dose was 140 micrograms/kg/minute and the intracoronary bolus dose was 15–20 micrograms to the right coronary artery and 18–24 micrograms to the left coronary artery. The two routes of administration were equally effective in measuring hyperemic flow, and adverse effects were limited to two patients who received intravenous adenosine; one patient had severe nausea and one patient with asthma had an episode of bronchospasm.

The use of intrathecal adenosine in patients with chronic neuropathic pain (35,45) has been briefly reviewed (46).

Drug–Drug Interactions

General

Adenosine does not interact with digoxin, disopyramide, flecainide, or quinidine.

Ciclosporin

Endogenous plasma adenosine concentrations were measured in 14 kidney transplant recipients taking ciclosporin and compared with five transplant recipients not taking ciclosporin, two taking sirolimus (FK506), six patients with chronic renal insufficiency, and ten controls (47). Plasma adenosine concentrations were significantly higher in those taking ciclosporin and sirolimus and in the patients taking ciclosporin the plasma adenosine concentrations correlated with serum ciclosporin concentrations. An in vitro study showed that ciclosporin inhibited the uptake of adenosine by erythrocytes. The authors concluded that since adenosine is immunosuppressant, the raised concentrations of adenosine in patients taking ciclosporin might contribute to the immunosuppressive action of ciclosporin. A further mechanism of the increase in adenosine concentration was possibly increased tissue release secondary to ciclosporin-induced vasoconstriction. The relevance of these results to the use of therapeutic intravenous adenosine in patients already taking ciclosporin is not clear.

Dipyridamole

Dipyridamole inhibits the uptake of adenosine by cells and so increases its effects; this causes a large reduction in the effective dose of adenosine (48).

Sirolimus

In two kidney transplant recipients taking sirolimus (FK506), plasma adenosine concentrations were significantly increased (47). The relevance of these results to the use of therapeutic intravenous adenosine in patients already taking sirolimus is not clear.

Xanthines

Antagonists at adenosine receptors should inhibit the action of adenosine, and indeed theophylline increases the dose of adenosine needed for conversion of supraventricular tachycardia (49).

Diagnosis of Adverse Drug Reactions

In 34 patients given midazolam or placebo in a double-blind study, midazolam significantly reduced patients' experiences of palpitation and chest pain but had no effects on other adverse events (50). These effects were probably due to amnesia rather than a true reduction in the incidence of adverse events, and it is uncertain that the benefit to harm ratio is worth while. However, the authors suggested that midazolam might be useful in patients who have previously had unpleasant adverse reactions to adenosine.

References

1. Camm AJ, Garratt CJ. Adenosine and supraventricular tachycardia. N Engl J Med 1991;325(23):1621–9.
2. Harper KJ. Adenosine in the acute treatment of PSVT. Drug Ther 1992;March:53–72.
3. Rankin AC, Brooks R, Ruskin JN, McGovern BA. Adenosine and the treatment of supraventricular tachycardia. Am J Med 1992;92(6):655–64.
4. Hori M, Kitakaze M. Adenosine, the heart, and coronary circulation. Hypertension 1991;18(5):565–74.
5. Rankin AC, Oldroyd KG, Chong E, Dow JW, Rae AP, Cobbe SM. Adenosine or adenosine triphosphate for supraventricular tachycardias? Comparative double-blind randomized study in patients with spontaneous or inducible arrhythmias. Am Heart J 1990;119(2 Pt 1):316–23.
6. Pennell DJ, Mavrogeni SI, Forbat SM, Karwatowski SP, Underwood SR. Adenosine combined with dynamic exercise for myocardial perfusion imaging. J Am Coll Cardiol 1995;25(6):1300–9.
7. O'Keefe JH Jr, Bateman TM, Handlin LR, Barnhart CS. Four- versus 6-minute infusion protocol for adenosine thallium-201 single photon emission computed tomography imaging. Am Heart J 1995;129(3):482–7.
8. Dimitriu AG, Nistor N, Russu G, Cristogel F, Streanga V, Varlam L. Value of intravenous ATP in the diagnosis and treatment of tachyarrhythmias in children. Rev Med Chir Soc Med Nat Iasi 1998;102(3–4):100–2.
9. Pfammatter JP, Bauersfeld U. Safety issues in the treatment of paediatric supraventricular tachycardias. Drug Saf 1998;18(5):345–56.
10. Sherwood MC, Lau KC, Sholler GF. Adenosine in the management of supraventricular tachycardia in children. J Paediatr Child Health 1998;34(1):53–6.
11. Bakshi F, Barzilay Z, Paret G. Adenosine in the diagnosis and treatment of narrow complex tachycardia in the pediatric intensive care unit. Heart Lung 1998;27(1):47–50.

12. Prabhu AS, Singh TP, Morrow WR, Muzik O, Di Carli MF. Safety and efficacy of intravenous adenosine for pharmacologic stress testing in children with aortic valve disease or Kawasaki disease. Am J Cardiol 1999;83(2):284–6.
13. Thomas GS, Prill NV, Majmundar H, Fabrizi RR, Thomas JJ, Hayashida C, Kothapalli S, Payne JL, Payne MM, Miyamoto MI. Treadmill exercise during adenosine infusion is safe, results in fewer adverse reactions, and improves myocardial perfusion image quality. J Nucl Cardiol 2000;7(5):439–46.
14. Elliott MD, Holly TA, Leonard SM, Hendel RC. Impact of an abbreviated adenosine protocol incorporating adjunctive treadmill exercise on adverse effects and image quality in patients undergoing stress myocardial perfusion imaging. J Nucl Cardiol 2000;7(6):584–9.
15. Mulla N, Karpawich PP. Ventricular fibrillation following adenosine therapy for supraventricular tachycardia in a neonate with concealed Wolff–Parkinson–White syndrome treated with digoxin. Pediatr Emerg Care 1995;11(4):238–9.
16. Strickberger SA, Man KC, Daoud EG, Goyal R, Brinkman K, Knight BP, Weiss R, Bahu M, Morady F. Adenosine-induced atrial arrhythmia: a prospective analysis. Ann Intern Med 1997;127(6):417–22.
17. Rae CP, Mansfield MD, Dryden C, Kinsella J. Analgesic effect of adenosine on ischaemic pain in human volunteers. Br J Anaesth 1999;82(3):427–8.
18. Garratt KN, Holmes DR Jr, Molina-Viamonte V, Reeder GS, Hodge DO, Bailey KR, Lobl JK, Laudon DA, Gibbons RJ. Intravenous adenosine and lidocaine in patients with acute mycocardial infarction. Am Heart J 1998;136(2):196–204.
19. Zarate E, Sa Rego MM, White PF, Duffy L, Shearer VE, Griffin JD, Whitten CW. Comparison of adenosine and remifentanil infusions as adjuvants to desflurane anesthesia. Anesthesiology 1999;90(4):956–63.
20. Christopher M, Key CB, Persse DE. Refractory asystole and death following the prehospital administration of adenosine. Prehosp Emerg Care 2000;4(2):196–8.
21. Knight BP, Zivin A, Souza J, Goyal R, Man KC, Strickberger A, Morady F. Use of adenosine in patients hospitalized in a university medical center. Am J Med 1998;105(4):275–80.
22. Jaeggi E, Chiu C, Hamilton R, Gilljam T, Gow R. Adenosine-induced atrial pro-arrhythmia in children. Can J Cardiol 1999;15(2):169–72.
23. Israel C, Klingenheben T, Gronefeld G, Hohnloser SH. Adenosine-induced atrial fibrillation. J Cardiovasc Electrophysiol 2000;11(7):825.
24. Kaplan IV, Kaplan AV, Fisher JD. Adenosine induced atrial fibrillation precipitating polymorphic ventricular tachycardia. Pacing Clin Electrophysiol 2000;23(1):140–1.
25. Misra D, Van Tosh A, Schweitzer P. Adenosine induced monomorphic ventricular tachycardia. Pacing Clin Electrophysiol 2000;23(6):1044–6.
26. Ruiz Ruiz MJ, Rivero Guerrero JA, Barrera Cordero A, de Teresa E. Empeoramiento de la taquicardia Supraventricular tras la administracion de adenosina: un efecto paradojico. [Worsening of supraventricular tachycardia after intravenous after adenosine administration: a paradoxical effect.] Med Clin (Barc) 2001;117(7):276.
27. Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Case report: adenosine induced ventricular fibrillation in a patient with stable ventricular tachycardia. J Interv Card Electrophysiol 2001;5(1):71–4.
28. Tan HL, Spekhorst HH, Peters RJ, Wilde AA. Adenosine induced ventricular arrhythmias in the emergency room. Pacing Clin Electrophysiol 2001;24(4 Pt 1):450–5.
29. Alkoutami GS, Reeves WC, Movahed A. The frequency of atrioventricular block during adenosine stress testing in young, middle-aged, young-old, and old-old adults. Am J Geriatr Cardiol 2001;10(3):159–61.
30. Toft J, Mortensen J, Hesse B. Risk of atrioventricular block during adenosine pharmacologic stress testing in heart transplant recipients. Am J Cardiol 1998;82(5):696–7.
31. Alkoutami GS, Reeves WC, Movahed A. The safety of adenosine pharmacologic stress testing in patients with first-degree atrioventricular block in the presence and absence of atrioventricular blocking medications. J Nucl Cardiol 1999;6(5):495–7.
32. Ng WH, Polosa R, Church MK. Adenosine bronchoconstriction in asthma: investigations into its possible mechanism of action. Br J Clin Pharmacol 1990;30(Suppl 1): S89–98.
33. Johnston DL, Scanlon PD, Hodge DO, Glynn RB, Hung JC, Gibbons RJ. Pulmonary function monitoring during adenosine myocardial perfusion scintigraphy in patients with chronic obstructive pulmonary disease. Mayo Clin Proc 1999;74(4):339–46.
34. Balan KK, Critchley M. Is the dyspnea during adenosine cardiac stress test caused by bronchospasm? Am Heart J 2001;142(1):142–5.
35. Belfrage M, Segerdahl M, Arner S, Sollevi A. The safety and efficacy of intrathecal adenosine in patients with chronic neuropathic pain. Anesth Analg 1999;89(1):136–42.
36. Eisenach JC, Hood DD, Curry R. Phase I safety assessment of intrathecal injection of an American formulation of adenosine in humans. Anesthesiology 2002;96(1):24–8.
37. Eisenach JC, Curry R, Hood DD. Dose response of intrathecal adenosine in experimental pain and allodynia. Anesthesiology 2002;97(4):938–42.
38. Rane K, Segerdahl M, Goiny M, Sollevi A. Intrathecal adenosine administration: a phase 1 clinical safety study in healthy volunteers, with additional evaluation of its influence on sensory thresholds and experimental pain. Anesthesiology 1998;89(5):1108–15.
39. Clarke KW, Brear SG, Hanley SP. Rise in intracranial pressure with intravenous adenosine. Lancet 1992; 339(8786):188–9.
40. Watt AH, Lewis DJ, Horne JJ, Smith PM. Reproduction of epigastric pain of duodenal ulceration by adenosine. BMJ (Clin Res Ed) 1987;294(6563):10–12.
41. Shaw AD, Boscoe MJ. Anaphylactic reaction following intravenous adenosine. Anaesthesia 1999;54(6):608.
42. Haynes BE. Two deaths after prehospital use of adenosine. J Emerg Med 2001;21(2):151–4.
43. Treuth MG, Reyes GA, He ZX, Cwajg E, Mahmarian JJ, Verani MS. Tolerance and diagnostic accuracy of an abbreviated adenosine infusion for myocardial scintigraphy: a randomized, prospective study. J Nucl Cardiol 2001;8(5):548–54.
44. Jeremias A, Whitbourn RJ, Filardo SD, Fitzgerald PJ, Cohen DJ, Tuzcu EM, Anderson WD, Abizaid AA, Mintz GS, Yeung AC, Kern MJ, Yock PG. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. Am Heart J 2000;140(4):651–7.
45. Sjolund KF, Segerdahl M, Sollevi A. Adenosine reduces secondary hyperalgesia in two human models of cutaneous inflammatory pain. Anesth Analg 1999;88(3):605–10.
46. Kopf A, Ruf W. Novel drugs for neuropathic pain. Curr Opin Anaesthesiol 2000;13:577–83.
47. Guieu R, Dussol B, Devaux C, Sampol J, Brunet P, Rochat H, Bechis G, Berland YF. Interactions between cyclosporine A and adenosine in kidney transplant recipients. Kidney Int 1998;53(1):200–4.
48. Watt AH, Bernard MS, Webster J, Passani SL, Stephens MR, Routledge PA. Intravenous adenosine in the treatment of supraventricular tachycardia: a dose-ranging study and interaction with dipyridamole. Br J Clin Pharmacol 1986;21(2):227–30.

49. diMarco JP, Sellers TD, Lerman BB, Greenberg ML, Berne RM, Belardinelli L. Diagnostic and therapeutic use of adenosine in patients with supraventricular tachyarrhythmias. J Am Coll Cardiol 1985;6(2):417–25.
50. Hourigan C, Safih S, Rogers I, Jacobs I, Lockney A. Randomized controlled trial of midazolam premedication to reduce the subjective adverse effects of adenosine. Emerg Med (Fremantle) 2001;13(1):51–6.

Adiphenine

General Information

Adiphenine, in the doses generally used (up to 60 mg/day), is of disputed value. It may have a non-specific relaxant action on the gastrointestinal muscle and some local anesthetic effect on the buccal mucosa. The evidence on its effects is meager and it seems like an anticholinergic drug that has been promoted in doses that are often too low to result in either a useful therapeutic effect or in adverse effects.

Adrenaline

See also Anticholinergic drugs

General Information

Note on nomenclature

Although epinephrine is the recommended International Non-proprietary Name (rINN), there are good reasons why the name adrenaline should be preferred, based on usage, history, etymology, and, most importantly, risk of clinical errors (1).

Adrenaline is a catecholamine with agonist effects at both α- and β-adrenoceptors.

The use of adrenaline is largely limited to subcutaneous administration for the immediate relief of anaphylactic shock. Intramuscular doses of 0.1 ml of a 1:1000 solution are often given repeatedly, up to a maximum of some 2 ml in 5 minutes. Although the sensitivity of individuals to adrenaline varies considerably, the adverse reactions to such doses are generally limited to mild cardiovascular effects.

Intravenous administration of adrenaline for treatment of systemic anaphylactic shock should be undertaken with extreme caution, even in patients without a history of cardiovascular disease. At all times the patient must be monitored and emergency treatment should be available. Even the infiltration of low doses of adrenaline for local hemostasis can be attended by these risks; one patient developed ventricular tachycardia and severe hypertension after receiving 3.75 mg locally for this purpose (SEDA-17, 160), and the value of this treatment is in any case today regarded as dubious (SEDA-17, 161).

Subcutaneous adrenaline has been used to prevent the immediate adverse effects of snake antivenom, although evidence of its efficacy is scanty (2). A large clinical trial is under way in Sri Lanka.

Adrenaline was at one time a component of asthma sprays, and dilated cardiomyopathy was described after many years of use (3).

Adrenaline has been largely abandoned as an adjuvant to local anesthetics, although in a 1:80 000 concentration it is still sometimes used in dental and in epidural anesthesia.

Dipivefrin

Dipivefrin (dipivalyl epinephrine) is a prodrug of adrenaline, used topically in the treatment of glaucoma. Its potential advantages include a longer duration of action, increased local availability, greater potency, greater stability, and fewer adverse effects. The effect on pupil size is insignificant, no objective sight-threatening effects are observed, and central visual acuity and visual fields are not affected after application of a 0.1% solution of dipivefrine. However, minor sporadic and transient burning or stinging sensations can occur.

Organs and Systems

Cardiovascular

When the limits of tolerance are approached, there may be palpitation, extra beats, and a rise in blood pressure. In sensitive individuals or at high doses, ventricular fibrillation, subarachnoid hemorrhage, and even hemiplegia have been known to occur. Adrenaline can occasionally cause pulmonary edema (4,5). It is possible that in at least some of these cases the drug has been inadvertently injected intravenously.

Ventricular dysrhythmias have been reported in a case of adrenaline overdose (6).

- A 5-year-old boy was given subcutaneous adrenaline 1:1000 after a severe allergic reaction to a bee sting. Inadvertently, 10 times the correct dose was given. He developed extra beats and two brief runs of ventricular tachycardia, but recovered fully after about 20 minutes. Creatine kinase activity, both total and the MB fraction, was slightly raised in this patient (total 603 IU/l, MB fraction 161 IU/l; upper limits of the local reference range 243 and 15 IU/l), suggesting cardiac damage.

Life-threatening torsade de pointes has been observed when an epidural anesthetic was given using 20 ml of bupivacaine containing only 1:200 000 adrenaline (7).

When adrenaline 0.4 ml of a 1 mg/ml solution was inadvertently injected into the penile skin of a 12-hour-old neonate the skin blanched and the error was immediately understood (8). After repeated doses of phentolamine (total 0.65 mg) the skin regained its normal color. There were no sequelae.

Adrenaline is occasionally used as a hemostatic agent, with rare complications. However, they do occur, as noted in a report from Lyon (9).

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Adiphenine

General Information

Adiphenine, in the doses generally used (up to 60 mg/day), is of disputed value. It may have a non-specific relaxant action on the gastrointestinal muscle and some local anesthetic effect on the buccal mucosa. The evidence on its effects is meager and it seems like an anticholinergic drug that has been promoted in doses that are often too low to result in either a useful therapeutic effect or in adverse effects.

Adrenaline

See also Anticholinergic drugs

General Information

Note on nomenclature

Although epinephrine is the recommended International Non-proprietary Name (rINN), there are good reasons why the name adrenaline should be preferred, based on usage, history, etymology, and, most importantly, risk of clinical errors (1).

Adrenaline is a catecholamine with agonist effects at both α- and β-adrenoceptors.

The use of adrenaline is largely limited to subcutaneous administration for the immediate relief of anaphylactic shock. Intramuscular doses of 0.1 ml of a 1:1000 solution are often given repeatedly, up to a maximum of some 2 ml in 5 minutes. Although the sensitivity of individuals to adrenaline varies considerably, the adverse reactions to such doses are generally limited to mild cardiovascular effects.

Intravenous administration of adrenaline for treatment of systemic anaphylactic shock should be undertaken with extreme caution, even in patients without a history of cardiovascular disease. At all times the patient must be monitored and emergency treatment should be available. Even the infiltration of low doses of adrenaline for local hemostasis can be attended by these risks; one patient developed ventricular tachycardia and severe hypertension after receiving 3.75 mg locally for this purpose (SEDA-17, 160), and the value of this treatment is in any case today regarded as dubious (SEDA-17, 161).

Subcutaneous adrenaline has been used to prevent the immediate adverse effects of snake antivenom, although evidence of its efficacy is scanty (2). A large clinical trial is under way in Sri Lanka.

Adrenaline was at one time a component of asthma sprays, and dilated cardiomyopathy was described after many years of use (3).

Adrenaline has been largely abandoned as an adjuvant to local anesthetics, although in a 1:80 000 concentration it is still sometimes used in dental and in epidural anesthesia.

Dipivefrin

Dipivefrin (dipivalyl epinephrine) is a prodrug of adrenaline, used topically in the treatment of glaucoma. Its potential advantages include a longer duration of action, increased local availability, greater potency, greater stability, and fewer adverse effects. The effect on pupil size is insignificant, no objective sight-threatening effects are observed, and central visual acuity and visual fields are not affected after application of a 0.1% solution of dipivefrine. However, minor sporadic and transient burning or stinging sensations can occur.

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Adrenaline is occasionally used as a hemostatic agent, with rare complications. However, they do occur, as noted in a report from Lyon (9).

- A 64-year-old man with diabetes and hypertension bled from a site in the lower rectum. A local injection of adrenaline 0.2 mg successfully stopped the hemorrhage, but very soon after he became hypotensive, with rapid atrial fibrillation (ventricular rate not given), the first time he had experienced this. He reverted spontaneously to sinus rhythm within 24 hours.

The authors suggested that if this type of procedure is contemplated in elderly patients with cardiovascular disease an anesthetist should be present to monitor cardiovascular status; it may in any case be wiser to avoid adrenaline altogether in favor of other means of hemostasis.

A more unusual site of adrenaline injection has been described in a Canadian report (10).

- A 79-year-old woman developed pituitary apoplexy in an adenomatous gland and was being prepared for *trans*-sphenoidal hypophysectomy. Topical adrenaline (1:1000) was applied to both nostrils and then 1.5 ml of 1% lidocaine containing 1:100 000 adrenaline was injected into the nasal mucosa. The blood pressure immediately rose from 100/50 to 230/148 mmHg and the pulse rate from 48 to 140/minute. Although she was treated immediately with esmolol and intravenous glyceryl trinitrate, resulting in normalization of her blood pressure, subsequent investigations showed that she had had a painless myocardial infarction. She made a full recovery after pituitary surgery.

The authors suggested that if adrenaline is to be used in such cases, even lower concentrations might be advisable. This is reasonable, although one also wonders in this case whether her blood pressure may have been lowered too rapidly.

Sensory systems

Melanic conjunctivocorneal pigmentation has been reported with an incidence of 30% with adrenaline (11,12).

Cystoid macular edema has been reported to occur in 2.8% of the patients receiving adrenaline especially in aphakic or pseudophakic eyes (13). Cystoid macular edema has also been seen after the use of dipivefrine, but in the classic case described in 1982 pretreatment with timolol maleate may have predisposed the eye to this complication (14).

Central retinal vein thrombosis occurred in a 75-year-old man 20 minutes after the ipsilateral insertion of a 1% adrenaline-soaked cotton wool stick (15). Unfortunately, his visual acuity did not improve.

Metabolism

Lactic acidosis has been observed, persisting for some hours after deliberate intravenous misuse of 20 mg adrenaline by an addict (SED-12, 308). Six of 19 patients who were given adrenaline for hypotension after undergoing cardiopulmonary bypass developed lactic acidosis, though the ultimate outcome was favorable (SEDA-22, 154).

Mouth and teeth

Facial swelling due to drug-induced sialadenosis was repeatedly observed in one patient who controlled her asthma symptoms with an adrenaline inhaler (SEDA-14, 119).

Susceptibility Factors

Cardiovascular

In susceptible individuals, an attack of angina pectoris can be precipitated by adrenaline, and in any form of cardiac disease caution is indicated; at one time an attempt was made to use high doses of adrenaline for the early treatment of ventricular fibrillation, but its pharmacological effects swing the balance against its use, the immediate survival rate actually being reduced.

Hyperthyroidism

Patients with hyperthyroidism are unduly sensitive to the effects of adrenaline (SEDA-14, 179).

Drug Administration

Drug administration route

While the absorption of adrenaline from a subcutaneous injection in healthy subjects is variable (and sometimes very slow) absorption from an inhaled dose is rapid and reliable (16). The main adverse effect from the inhaled route, for example in a dose of 3–4.5 mg, is gastrointestinal discomfort, with nausea and sometimes vomiting; this seems to be a local effect since it does not occur with injections. However, both forms produce mild tremor and palpitation in some individuals.

Since adrenaline is so short acting, the metabolic and other adrenergic effects which it can produce are unlikely to be elicited unless a depot formulation is used; in the latter event, hyperglycemia may occur.

Drug–Drug Interactions

Beta-adrenoceptor antagonists

Small quantities of adrenaline, such as are present as an additive in local anesthetic formulations, can be dangerously potentiated by beta-adrenoceptor blockers; propranolol should be discontinued at least 3 days in advance of administering such products for local anesthesia. A combined infusion of adrenaline and propranolol has been used for diagnosing insulin resistance, but it can evoke cardiac dysrhythmias, even in patients without signs of coronary disease (17).

Halothane

Halothane and some other anesthetics sensitize patients to the risk of adrenaline-induced ventricular dysrhythmias and acute pulmonary edema, especially if hypoxia is present (18,19).

Hyaluronidase

Adrenaline is physically incompatible with hyaluronidase (20).

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors have been said to potentiate the hypertensive effects of adrenaline, but there is no good clinical evidence of such an interaction (21). Nevertheless, care should be taken when contemplating the use of adrenaline in patients taking a monoamine oxidase inhibitor.

Sodium novobiocin

Adrenaline is physically incompatible with sodium novobiocin (20).

Sodium warfarin

Adrenaline is physically incompatible with sodium warfarin (20).

Tricyclic antidepressants

Tricyclic antidepressants inhibit the uptake of catecholamines, such as adrenaline, into sympathetic neurons and can enhance the cardiovascular effects, so that even the small amounts of adrenaline present as additives in some local anesthetics can have a marked effect on the cardiovascular system.

References

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2. Nuchpraryoon I, Garner P. Interventions for preventing reactions to snake antivenom. Cochrane Database Syst Rev 2000:(2):CD002153. http://www.update-software.com/abstracts/ab002153.htm.
3. Stewart MJ, Fraser DM, Boon N. Dilated cardiomyopathy associated with chronic overuse of an adrenaline inhaler. Br Heart J 1992;68(2):221–2.
4. Worthen M, Placik B, Argano B, MacCanon DM, Luisada AA. On the mechanism of epinephrine-induced pulmonary edema. Jpn Heart J 1969;10(2):133–41.
5. Ersoz N, Finestone SC. Adrenaline-induced pulmonary oedema and its treatment. A report of two cases. Br J Anaesth 1971;43(7):709–12.
6. Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. Pediatr Emerg Care 1999;15(2):116–18.
7. Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M, Lazzara R. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 1988;31(2):115–72.
8. Adams MC, McLaughlin KP, Rink RC. Inadvertent concentrated epinephrine injection at newborn circumcision: effect and treatment. J Urol 2000;163(2):592.
9. Galoo E, Godon P, Potier V, Vergeau B. Fibrillation auriculaire compliquant une hémostase endoscopique rectale par injection d' adrénaline. [Atrial fibrillation following a rectal endoscopic injection using epiphedrine solution.] Gastroenterol Clin Biol 2002;26(1):99–100.
10. Chelliah YR, Manninen PH. Hazards of epinephrine in transsphenoidal pituitary surgery. J Neurosurg Anesthesiol 2002;14(1):43–6.
11. Macho MS, Vicente MC, Salorio MS. Depositos pigmentarios conjunctivales producidos por epinefrina. [Conjunctival pigmentary deposits produced by epinephrine.] Arch Soc Esp Oftalmol 1973;33:537.
12. Zolog N, Leibovici M. La "mélanose" conjonctivale par épinéphrine. [Conjunctival melanosis caused by epinephrine.] Bull Mem Soc Fr Ophtalmol 1973;86(0):198–200.
13. Larricart P. Les affections retiniennes. [Retinal diseases.] Bull Soc Ophtalmol Fr 1985;Spec No:193–211.
14. Mehelas TJ, Kollarits CR, Martin WG. Cystoid macular edema presumably induced by dipivefrin hydrochloride (Propine). Am J Ophthalmol 1982;94(5):682.
15. Maaranen TH, Mantyjarvi MI. Central retinal artery occlusion after a local anesthetic with adrenaline on nasal mucosa. J Neuroophthalmol 2000;20(4):234–5.
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17. Lampman RM, Santinga JT, Bassett DR, Savage PJ. Cardiac arrhythmias during epinephrine–propranolol infusions for measurement of in vivo insulin resistance. Diabetes 1981;30(7):618–20.
18. Mattig W, Radam R. Todesfall nach Adrenalinanwendung unter Halothannarkose. Dtsch Gesundheitsw 1977;32:953.
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Adrenoceptor agonists

See also Individual agents

General Information

Adrenoceptor agonists evoke physiological responses similar to those produced by stimulation of adrenergic nerves or the physiological release of adrenaline (see Table 1). For many of these responses it is currently possible to conclude that only an alpha-adrenoceptor or a beta-adrenoceptor is involved, and in some cases one can distinguish a $beta_1$ from a $beta_2$ response. In some cases, however, the distinction is not clear: most adrenoceptor agonists, however specific to a particular receptor type they are claimed to be, will for example on occasion stimulate central nervous functions, resulting in nervousness, insomnia, tremors, dizziness, or headache. In some organ systems both alpha-adrenoceptors and beta-adrenoceptors are present; thus, the nature of the response produced will depend either on the concentrations achieved or on other factors; whether, for example, the uterus contracts or relaxes in response to an adrenergic drug depends in part on the hormonal balance in the system at that moment.

Alpha-adrenoceptor agonists, such as clonidine, are little used nowadays in the treatment of hypertension or migraine. Clonidine is used epidurally, in combination with opioids, neostigmine, and anesthetic and analgesic agents, to produce segmental analgesia, particularly for postoperative relief of pain after obstetrical and surgical

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Table 1 Adrenoceptors and the effects of agonists

Organs and systems	Receptor	Response to an agonist
Cardiovascular		
Heart		
Sinoatrial node	β_1	Increased heart rate
Atria	β_1	Increased contractility and conduction velocity
Atrioventricular node and conduction system	β_1	Increased conduction velocity and automaticity
Ventricles	β_1	Increased contractility, conduction velocity, automaticity, rate of idiopathic pacemakers
Blood vessels		
Coronary	α, β_2	Constriction
Skin, mucosa	α	Constriction
Skeletal muscle	α or β_2	Constriction or dilatation
Cerebral	α	Slight constriction
Pulmonary	α or β_2	Constriction or dilatation
Abdominal viscera	α or β_2	Constriction or dilatation
Salivary glands	α	Constriction
Respiratory		
Bronchial muscle	β_2	Relaxation
Bronchial glands	α_1, β_2	Decreased or increased secretion
Nervous system		
Cerebral function	Various	Stimulation
Eyes		
Radial muscle, iris	α	Contraction (mydriasis)
Ciliary muscle	β	Relaxation for far vision (slight)
Hematologic		
Spleen capsule	α	Contraction
Salivary glands	α_1	Potassium and water secretion
	β	Amylase secretion
Gastrointestinal		
Motility and tone	α_1, β_1, β_2	Decrease (usually)
Sphincters	α	Contraction (usually)
Secretion of various substances	Various	Inhibition
Liver		
Glycogenolysis and gluconeogenesis	α_1, β_2	Stimulation
Gallbladder		
Bile ducts	β_2	Relaxation
Urinary tract		
Ureter; tone, motility	β_2	Relaxation (usually)
Bladder; detrusor	β	Relaxation (usually)
Trigone, sphincter	α	Contraction
Renal vessels	α_1, β_1, β_2	Primary contraction
Skin		
Pilomotor muscles	α	Contraction
Sweat glands	α	Slight local secretion
Musculoskeletal		
Muscle glycogenolysis	β	Stimulation
Sexual function		
Uterus	α, β_2	Variable effect[a]
Male sex function	α_1	Ejaculation

[a] Response depends inter alia on hormonal status.

procedures. Apraclonidine is available for the short-term reduction of intraocular pressure.

The drugs that were developed some 40 years ago as general beta-adrenoceptor agonists have largely fallen into disuse with the development of more selective beta$_1$-adrenoceptor agonists (for use in cardiac failure) and beta$_2$-adrenoceptor agonists (for use in airways disease and threatened premature labor).

Beta$_3$-adrenoceptor agonists

Stimulation of beta-adrenoceptors on the cell surface of adipocytes promotes lipolysis and energy expenditure. These receptors are neither beta$_1$-adrenoceptors nor beta$_2$-adrenoceptors, and they have been termed atypical or beta$_3$-adrenoceptors. Some atypical agonists (BRL 26830 A, BRL 35135, CL 316243, and D 7114) have been developed and assessed for their ability to stimulate

these receptors and hence to induce weight loss. The BRL compounds appear to exaggerate physiological tremor, presumably through an effect on $beta_2$-adrenoceptors; the two other compounds are said to be more selective.

Ajmaline and its derivatives

See also Antidysrhythmic drugs

General Information

Ajmaline and its derivatives, prajmalium bitartrate (rINN; *N*-propylajmaline), lorajmine (rINN; chloroacetylajmaline), detajmium bitartrate (rINN), and diethylaminohydroxypropylajmaline, are *Rauwolfia* alkaloids. Their use is restricted by serious adverse effects, such as neutropenia and cardiac dysrhythmias, which have been reviewed (1). Other adverse effects include dizziness, headache, and a sensation of warmth after intravenous injection.

Organs and Systems

Cardiovascular

Ajmaline occasionally causes cardiac dysrhythmias (SEDA-17, 219). Of 1995 patients who were given ajmaline 1 mg/kg intravenously during an electrophysiological study, 63 developed a supraventricular tachydysrhythmia (atrial flutter, fibrillation, or tachycardia), and seven an atrioventricular re-entrant tachycardia (2). Those most at risk were older patients, those with underlying cardiac disease, and those with a history of dysrhythmias or sinus node dysfunction.

Two cases of torsade de pointes have been reported in association with prolongation of the QT interval (3). Polymorphous ventricular tachycardia has been reported in three cases (4–6).

- A 13-year-old boy with Brugada syndrome (right bundle branch block with persistent ST segment elevation) was given an injection of ajmaline 1 mg/kg and developed greater ST segment elevation and more marked right bundle branch block morphology (7). This was followed by short runs of non-sustained polymorphic ventricular tachycardia, gradually increasing until monomorphic ventricular tachycardia occurred. The dysrhythmia eventually resolved without further treatment.

It is unwise to give antidysrhythmic drugs to patients with Brugada syndrome.

Nervous system

Neurological effects have occasionally been reported in patients taking ajmaline derivatives; they include confusion and cranial nerve palsies (8,9).

Hematologic

Neutropenia is a relatively common and important adverse effect of ajmaline (10). Of the three main mechanisms that cause neutropenia (immune, toxic, and autoimmune) two have been associated with ajmaline: immune and autoimmune neutropenia.

Liver

Ajmaline can cause hepatitis or cholestasis. Cholestasis has been reported in association with neutropenia (11) and with fever and eosinophilia (12). Although acute liver damage due to ajmaline is usually reversible, there has been a report of persistent jaundice due to long-lasting cholestasis (13).

Immunologic

Hypersensitivity to ajmaline is rare, but there has been a report of an immune interstitial nephritis in association with fever (14).

Drug Administration

Drug overdose

In overdosage ajmaline can cause heart block and dysrhythmias, hypotension, malaise, vertigo, respiratory depression, and coma (15). In one series of 38 cases there were nine deaths (24%) (16). Treatment of overdosage includes the intravenous administration of molar sodium lactate for dysrhythmias, conduction disturbances, and circulatory failure; a pacemaker may be required.

- After an overdose of detajmium bitartrate in a dose of 18 mg/kg, a 36-year-old woman developed ventricular flutter, which responded to treatment with lidocaine, defibrillation, glucagon, noradrenaline, and sodium chloride (17). Hypokalemia responded to intravenous potassium chloride.
- A 57-year-old man took ajmaline 1000 mg with suicidal intent (18). He was unconscious and hypotensive and had serious disturbances in cardiac conduction. His serum and urine ajmaline concentrations were high. Although only 4% of the ingested dose was excreted following forced diuresis, all evidence of toxicity disappeared within 21 hours.

Various types of cardiac dysrhythmia have previously been reported after overdosage of ajmaline (SEDA-2, 162).

References

1. Schwartz JB, Keefe D, Harrison DC. Adverse effects of antiarrhythmic drugs. Drugs 1981;21(1):23–45.
2. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. Int J Cardiol 1992;34(2):189–98.
3. Haverkamp W, Monnig G, Kirchhof P, Eckardt L, Borggrefe M, Breithardt G. Torsade de pointes induced by ajmaline. Z Kardiol 2001;90(8):586–90.
4. Kaul U, Mohan JC, Narula J, Nath CS, Bhatia ML. Ajmaline-induced torsade de pointes. Cardiology 1985;72(3):140–3.
5. Kolar J, Humhal J, Karetova D, Novak M. "Torsade de pointes" po mezokainu a ajmalinu u nemocne s intermitertni sinokomorovou blokadou. Priznivy recebny vliv vysokych davek izoprenalinu. [Torsade de pointes after mesocaine and ajmaline in a patient with intermittent atrioventricular block. Favorable therapeutic effect of high doses of isoprenaline.] Cas Lek Cesk 1987;126(48):1503–7.

these receptors and hence to induce weight loss. The BRL compounds appear to exaggerate physiological tremor, presumably through an effect on $beta_2$-adrenoceptors; the two other compounds are said to be more selective.

Ajmaline and its derivatives

See also Antidysrhythmic drugs

General Information

Ajmaline and its derivatives, prajmalium bitartrate (rINN; *N*-propylajmaline), lorajmine (rINN; chloroacetylajmaline), detajmium bitartrate (rINN), and diethylaminohydroxypropylajmaline, are *Rauwolfia* alkaloids. Their use is restricted by serious adverse effects, such as neutropenia and cardiac dysrhythmias, which have been reviewed (1). Other adverse effects include dizziness, headache, and a sensation of warmth after intravenous injection.

Organs and Systems

Cardiovascular

Ajmaline occasionally causes cardiac dysrhythmias (SEDA-17, 219). Of 1995 patients who were given ajmaline 1 mg/kg intravenously during an electrophysiological study, 63 developed a supraventricular tachydysrhythmia (atrial flutter, fibrillation, or tachycardia), and seven an atrioventricular re-entrant tachycardia (2). Those most at risk were older patients, those with underlying cardiac disease, and those with a history of dysrhythmias or sinus node dysfunction.

Two cases of torsade de pointes have been reported in association with prolongation of the QT interval (3). Polymorphous ventricular tachycardia has been reported in three cases (4–6).

- A 13-year-old boy with Brugada syndrome (right bundle branch block with persistent ST segment elevation) was given an injection of ajmaline 1 mg/kg and developed greater ST segment elevation and more marked right bundle branch block morphology (7). This was followed by short runs of non-sustained polymorphic ventricular tachycardia, gradually increasing until monomorphic ventricular tachycardia occurred. The dysrhythmia eventually resolved without further treatment.

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2. Brembilla-Perrot B, Terrier de la Chaise A. Provocation of supraventricular tachycardias by an intravenous class I antiarrhythmic drug. Int J Cardiol 1992;34(2):189–98.
3. Haverkamp W, Monnig G, Kirchhof P, Eckardt L, Borggrefe M, Breithardt G. Torsade de pointes induced by ajmaline. Z Kardiol 2001;90(8):586–90.
4. Kaul U, Mohan JC, Narula J, Nath CS, Bhatia ML. Ajmaline-induced torsade de pointes. Cardiology 1985;72(3):140–3.
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6. Schmitt C, Brachmann J, Schols W, Beyer T, Kubler W. Proarrhythmischer Effekt von Ajmalin bei idiopathischer ventrikulärer Tachykardie. [Proarrhythmic effect of ajmaline in idiopathic ventricular tachycardia.] Dtsch Med Wochenschr 1989;114(3):99–102.
7. Pinar Bermudez E, Garcia-Alberola A, Martinez Sanchez J, Sanchez Munoz JJ, Valdes Chavarri M. Spontaneous sustained monomorphic ventricular tachycardia after administration of ajmaline in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2000;23(3):407–9.
8. Aquaro G, Marra S, Paolillo V, Pavia M. Complicanze neurologiche in corso di terapia con 17-MDCAA. [Neurological complications during therapy with 17 MDCAA.] G Ital Cardiol 1977;7(3):304–8.
9. Lessing JB, Copperman IJ. Severe cerebral confusion produced by prajmalium bitartrate. BMJ 1977;2(6088):675.
10. Brna TG Jr. Agranulocytosis from antiarrhythmic agents. What to watch for when a medication is first prescribed. Postgrad Med 1991;89(1):181–8.
11. Offenstadt G, Boisante L, Onimus R, Amstutz P. Agranulocytose et hepatite cholestatique au cours d'un traitement par l'ajmaline. [Agranulocytosis and cholestatic hepatitis during treatment with ajmaline.] Ann Med Interne (Paris) 1976;127(8–9):622–7.
12. Buscher HP, Talke H, Rademacher HP, Gessner U, Oehlert W, Gerok W. Intrahepatische Cholestase durch N-Propyl-Ajmalin. [Intrahepatic cholestasis due to N-propyl ajmaline.] Dtsch Med Wochenschr 1976;101(18):699–703.
13. Chammartin F, Levillain P, Silvain C, Chauvin C, Beauchant M. Hepatite prolongée a l'ajmaline—description d'un cas et revue de la litterature. [Prolonged hepatitis due to ajmaline—description of a case and review of the literature.] Schweiz Rundsch Med Prax 1989;78(20):582–4.
14. Dupond JL, Herve P, Saint-Hillier Y, Guyon B, Colas JM, Perol C, Leconte des Floris R. Anurie recidivant a 3 reprises; complication exceptionelle d'un traitement antiarythmique. J Med Besancon 1975;11:231.
15. Tempe JD, Jaeger A, Beissel J, Burg E, Mantz JM. Intoxications aigués par trois drogues cardiotropes: l'ajmaline, la chloroquine, la digitaline. J Med Strasbourg (Eur Med) 1976;7:569.
16. Conso F, Bismuth C, Riboulet G, Efthymiou ML. Intoxication aiguë par l'ajmaline. [Acute poisoning by ajmaline.] Therapie 1979;34(4):529–30.
17. Mobis A, Minz DH. Suizidale Tachmalcor-Intoxikation–Ein Fallbericht. [Suicidal Tachmalcor poisoning—a case report.] Anaesthesiol Reanim 1999;24(4):109–10.
18. Almog C, Maidan A, Pik A, Schlesinger Z. Acute intoxication with ajmaline. Isr J Med Sci 1979;15(7):570–2.

Alatrofloxacin and trovafloxacin

See also Fluoroquinolones

General Information

Alatrofloxacin is a fluoronaphthyridone that is hydrolysed to the active moiety, trovafloxacin, after intravenous administration. This fourth-generation broad-spectrum fluoroquinolone has activity against Gram-positive, Gram-negative, anerobic, and atypical respiratory pathogens. Because it has significant hepatotoxicity, the list of appropriate indications for trovafloxacin has been restricted.

In a multicenter, double-blind, randomized comparison of trovafloxacin 200 mg and clarithromycin 500 mg bd in 176 subjects with acute exacerbations of chronic bronchitis, the most common adverse effects of trovafloxacin were nausea (5%), dizziness (5%), vomiting (3%), and constipation (3%) (1). Because trovafloxacin is hepatotoxic, the list of appropriate indications has been limited to patients who have at least one of several specified infections, such as nosocomial pneumonia or complicated intra-abdominal infections that are serious and life- or limb-threatening in the physician's judgement.

Trovafloxacin may down-regulate cytokine mRNA transcription in human peripheral blood mononuclear cells stimulated with lipopolysaccharide or lipoteichoic acid (2). Likewise, trovafloxacin inhibited *Salmonella typhimurium*-induced production of TNFα, HIV-1 replication, and reactivation of latent HIV-1 in promonocytic U1 cells at concentrations comparable to the plasma and tissue concentrations achieved by therapeutic dosages (3).

Organs and Systems

Cardiovascular

Phlebitis can occur during parenteral administration of trovafloxacin. High concentrations of trovafloxacin (2 mg/ml) significantly reduced intracellular ATP content in cultured endothelial cells and reduced concentrations of ADP, GTP, and GDP (4). These in vitro data suggest that high doses of trovafloxacin are not compatible with maintenance of endothelial cell function and may explain the occurrence of phlebitis. Commercial formulations should be diluted and given into large veins.

Nervous system

Alatrofloxacin can cause seizures (5).

- A 37-year-old Asian man received several antibiotics (including intravenous ceftazidime, gentamicin, meropenem, metronidazole, and vancomycin) postoperatively. After 3 weeks he was given alatrofloxacin 75 mg in 25 ml of dextrose 5% (1.875 mg/ml) and developed generalized clonus. On rechallenge, infusing at half the initial rate, the seizure recurred. A CT scan of the brain was normal.

Seizures are rare but have occurred during treatment with other fluoroquinolones. This is the first report of a case of seizures associated with slow infusion of alatrofloxacin. However, as of 21 June 2000, the manufacturers had received 53 reports of seizures through worldwide postmarketing surveillance. In rat hippocampus slices, trovafloxacin had significant convulsive potential; the underlying mechanism is hitherto incompletely understood.

Trovafloxacin has been associated with diffuse weakness due to a demyelinating polyneuropathy in a patient without an underlying neurological disorder (6).

Hematologic

Alatrofloxacin has been associated with severe leukopenia (7).

- A 79-year-old white man was treated with intravenous alatrofloxacin mesylate 200 mg bd for 5 days. His

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