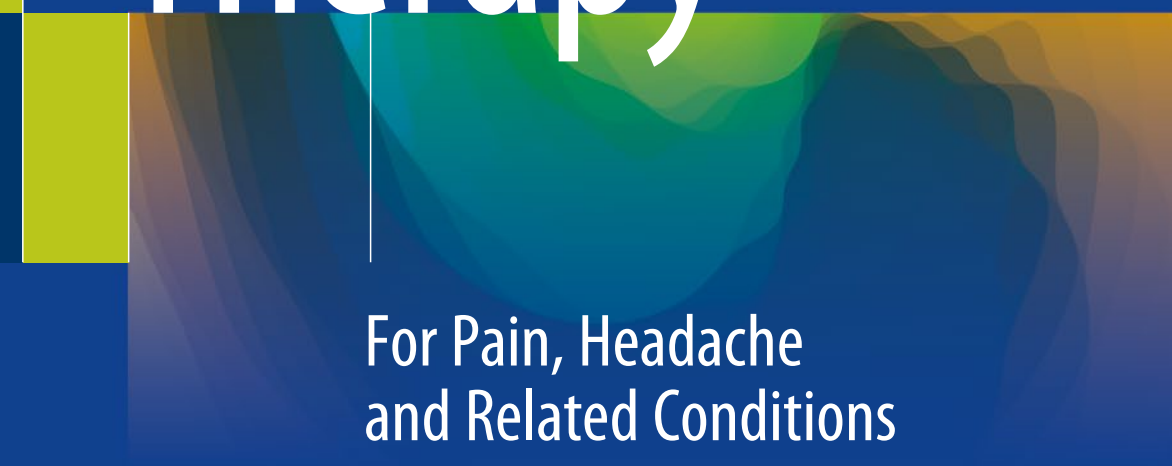
Infusion Therapy



For Pain, Headache and Related Conditions

Alaa Abd-Elsayed
Editor

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I would like to dedicate this book to my parents, my wife and my two beautiful kids Maro and George

Preface

Dear Reader:

I have found various infusional therapies to be increasingly useful in my pain management practice, and many patients who had failed other types of treatments responded to this modality. As my use of infusional treatments for pain has expanded, so has my awareness of the limitations on guidance for this type of treatment. In many cases, the use of a specific drug as an intravenous or subcutaneous is not a part of the FDA-approved labeling of the drug. In other instances, the use of a drug parenterally may be accepted and approved, yet the reason for the use of the drug is not part of the labeling. An example is the increasing use of intravenous lidocaine for the treatment of pain instead of its formally approved use for cardiac arrhythmias. Rigorous blinded and controlled studies may not be supported for drugs that are generic and relatively inexpensive, so in many cases one's off-label use of an infusional therapy is based upon reported cases or case series. In addition, the novel application of drugs to diseases outside of our typical practice may provide insight into how the drugs might have application to our own patient population.

The goal of this book is to provide an overview of various intravenously infused medications that can serve as a summary of current practice. In many examples in this book, the applications and use of the drugs are familiar and FDA-approved. In others, often with the same drugs, the authors seek to provide a summary of less formalized, yet hopefully useful applications of the medications. A brief overview of the pharmacology of the drugs is provided, which may provide both useful review and education on newer mechanistic discoveries that support the use of the medication. Monitoring guidelines, typical doses and titration processes, and cautions are included as well, with the intent of providing the practitioner a useful resource for their practice.

It should be cautioned that the off-label use of infusional therapies may meet resistance by insurers of health care. While a publication such as this may provide support for reimbursement for the off-label use of a medication, consideration of the financial impact of novel infusional treatments may be necessary on an individual basis.

Finally, like all publications, this is a work that reflects practice at a point in time. While the authors here present their best interpretation and recommendations for

the use of medications covered in the various chapters, it must be recognized by the reader that much of this practice will change over time. Professional judgement must prevail on behalf of the individual patient.

Madison, WI, USA Alaa Abd-Elsayed

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Paul R. Hutson and Alaa Abd-Elsayed

Introduction

Lidocaine is an amide local anesthetic that was found in the 1950s to have antiarrhythmic effects when infused intravenously. Lidocaine is still used for this purpose but is usually reserved for patients with ventricular arrhythmias who fail to adequately respond to amiodarone [1]. In current practice, intravenous infusions of lidocaine are more commonly used for the treatment of neuropathic pain. Local infiltrations are obviously used for pre-procedural anesthesia and may be used post-procedure to decrease pain and the need for opioid analgesics. Lidocaine may also be used topically, such as with cutaneous patches, or as an oral rinse for patients with pain from mucositis.

Lidocaine is metabolized by CYP1A2 and CYP3A4 in the liver to its active metabolites MEGX, glycinexylidide (GX), and N-ethylglycine (EG) [2, 3]. MEGX is considered to have slightly less activity than lidocaine as an inhibitor of the Na-channel [2]. MEGX and the other metabolites are considered to have greater analgesic effects on other pathways of neurotransmission such as the glycine receptor than does the parent drug.

Dosing adjustments are not needed in the presence of mild-moderate renal impairment, and even patients who demonstrate severe impairment of kidney function may benefit from a single dose of systemic lidocaine for neuropathic pain that has been reduced by 50% [4, 5].

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Mechanism of Action

Lidocaine is known to be an inhibitor of the voltage-gated sodium (Na) channel (VGSC) of both peripheral nociceptive and dorsal root neurons [6, 7]. The action of lidocaine and its active metabolite (MEGX) upon the VGSC leads to an inhibition of depolarization and hence an inhibition of neurotransmission. It is this inhibition of the VGSC that is considered to provide the antiarrhythmic action of lidocaine [2]. MEGX is considered to have approximately 80% of the activity of lidocaine in inhibiting the VGSC. The potency of the GX and N-ethylglycine (EG) in inhibiting the VGSC is less well characterized, but is considered to be minimal.

In addition to the inhibition of the VGSC, other mechanisms of action may be responsible for the anti-nociceptive and analgesic effects of lidocaine. MEGX, GX, and EG were all found in *in vitro* models to inhibit the uptake of the neurotransmitter amino acid glycine by the GlyT1 glycine transporter [8]. The inhibition of GlyT1 by GX and EG was shown to be competitive, whereas the concentration-dependent inhibition by MEGX was more mechanistic. The increase in synaptic glycine is suggested to decrease hyperalgesia and neuropathic pain by action at spinal inhibitory glycine receptors [8].

Lidocaine also demonstrates anti-inflammatory effects, but it is not clear to what extent the parent drug is responsible for these effects as opposed to the action of the metabolites. Doses of lidocaine have been shown to decrease granulocyte adhesion, migration, and activation [9]. Effects upon cyclooxygenase are not well described.

Indications

FDA-approved labeling includes its use for local and regional nerve blocks by local infiltration. Lidocaine hydrochloride injection administered intravenously or intramuscularly is also indicated in the acute management of ventricular arrhythmias such as those occurring in relation to acute myocardial infarction, or during cardiac manipulation, such as cardiac surgery [1, 10]. There is no formal FDA-approved indication for the intravenous administration of lidocaine for the treatment of pain. Although this does not prevent the use of lidocaine for this purpose, it may complicate the reimbursement for such use.

Post-herpetic and Peripheral Neuropathic Pain

The use of short IV infusions of lidocaine has been shown to decrease pain scores or the area of allodynia in patients with nerve injury or host-herpetic neuralgia [11–15]. A 2005 Cochrane review found that the preponderance of the evidence from evaluable studies indicated that systemic (IV) lidocaine provided statistically significant improvement in pain [16]. The Cochrane review was impaired by a variety of sources of neuropathic pain that included post-herpetic pain, traumatic nerve injury, neuropathy secondary to cancer, and diabetes. No studies with extended

infusions have been reported for this use, and the duration of any benefit appears to be short, often returning to baseline within 24 hours.

Wallace found that concentrations of at least 1.5 mcg/mL were associated with an analgesic response (pain VAS and mechanical allodynia) with a multi-dose concentration-targeted infusion study [17]. This was an unusual approach to dose escalation, contrasting with other studies that tested different doses or infusion rates [18]. None of the clinical trials reviewed by Challapalli et al. in the Cochrane meta-analysis [16] appeared to administer a sustained, multiple-day infusion of lidocaine.

Attal and colleagues compared the effect of 5 mg/kg lidocaine infused over 30 minutes to placebo in 22 adults with post-herpetic neuralgia or peripheral nerve injury and found a significant difference in relief from spontaneous pain that lasted up to 6 hours [19]. The response to lidocaine was greatest in patients with substantial mechanical allodynia. Attal et al. also found that the administration of oral mexiletine yielded a higher analgesic benefit in patients with mechanical allodynia associated with their neuropathy [19]. Similarly, an analgesic response to IV lidocaine predicts a benefit from orally administered mexiletine used as a form of outpatient maintenance of the analgesia [20].

In a double-blind comparison of placebo vs lidocaine doses of 1 and 5 mg/kg infused over 2 hours, Baranowski found that there was no difference in either spontaneous or evoked pain between any of the three treatment arms [14]. However, the area of any allodynia decreased after the lidocaine treatments, and there was not a significantly greater effect with the higher dose of lidocaine. In contrast, Tremont-Lukats et al. noted that there appeared to be a significant difference in the response to peripheral nerve pain or CRPS when lidocaine was infused over 6 hours at 5 mg/kg, but not at 1 or 3 mg/kg [18]. This was a double-blinded but parallel arm study, and it is not known what impact the longer, 6-hour infusion may have played in the response.

Some patients find relief from post-herpetic neuralgia using 5% lidocaine patches or plasters that can correctly be assumed to deliver lidocaine at a rather constant rate similar to an IV or subcutaneous infusion. Pharmacokinetic sampling in patients with varying numbers of such topical dosages of lidocaine suggests that plasma concentrations are substantially lower than those achieved by typical doses of intravenous lidocaine infusions [21].

Complex Regional Pain Syndrome

Several case series suggest a benefit from more prolonged exposure to systemic lidocaine in some patients with Complex Regional Pain Syndrome (CRPS) [11, 22]. Linchitz reported a series of nine patients with a duration of CRPS of 30–96 months [22]. Four of the nine subjects were not able to complete the treatment, two for lidocaine hypersensitivity, and two for what were termed unrelated causes. The five remaining patients received a subcutaneous infusion of lidocaine at an initial rate of 200 mg/hr for 1 hour, followed by an infusion of 100–190 mg lidocaine per hour.

The SC lidocaine was continued for 4–5 days after the maximal decrease in pain expressed by the subject. Durable responses were found with these prolonged infusions, and patients could restart the infusions at home if pain recurred. The authors suggest that the response and durability of the response was due to the extended duration of the infusion compared to the typical 30–60 minute IV infusion. There was no apparent benefit of the subcutaneous route other than the convenience and safety of this route compared to IV dosing.

Similar to the 5-day subcutaneous lidocaine infusion reported by Lipchitz, Schwartzman et al. published a retrospective case series of 49 patients suffering from CRPS who received a 5-day IV infusion of lidocaine titrated to a concentration in plasma of 5 mg/L [23]. Seventy-six percent of the subjects reported at least a 25% reduction in pain score on the 0–10 NRS, and 31% reported more than a 50% reduction in NRS pain score. Other components of CRPS such as allodynia, cold sensitivity, and muscle weakness and spasms also improved to a statistically significant degree. The improvement in the pain and other CRPS-associated symptoms was maintained for 3 months, but after 6 months was no longer statistically significant. The intent was to establish a plasma lidocaine concentration of 5 mg/L, yet at the end of the 5-day IV infusion the mean lidocaine concentration was only 3.4 ± 1.3 mg/L. The concentrations of MEGX and other lidocaine metabolites were not mentioned [23].

Erythromelalgia

Erythromelalgia is a rare disease characterized by red, painful extremities. The symptoms may be intermittent, and affected patients will often try to decrease the pain and burning sensation by immersing the extremity in cold or iced water. Various pharmacologic interventions have been reported in multiple case series. Intravenous lidocaine has been reported to be helpful in an 11 year old boy for whom other drug treatments had failed [24]. Lidocaine infusion was begun at 16.5 mcg/kg/minute, and titrated upward to establish plasma lidocaine concentrations of 2–5 mg/L. After the pain was suppressed so that he had 4 nights of restful sleep, the lidocaine infusion was stopped and replaced with oral mexiletine, another inhibitor of the VGSC. The child is described to have had a durable remission of the pain with mexiletine concentrations of 0.7–1.4 mg/L. Recent data suggest that the responsiveness of erythromelalgia pain to lidocaine and mexiletine may be a function of the specific polymorphisms of the sodium channels associated with this disease [25].

Fibromyalgia

Three reports of the use of intravenous lidocaine suggest benefit in some patients diagnosed with fibromyalgia. A study of 5 mg/kg lidocaine infused over 30 minutes in 12 adult patients showed a durable reduction in pain for 4–7 days in patients who had a response [26]. The drug was well tolerated, and in some cases allowed

improvement in muscle strength. Raphael et al. prospectively and retrospectively reviewed the cases of 156 fibromyalgia patients who received lidocaine as short infusions over 6 consecutive days in increasing doses [27]. There were 42 minor side effects noted, most commonly hypotension, and one patient in the 106 subjects evaluated prospectively developed supraventricular tachycardia. Another experienced pulmonary edema, yet all the adverse events resolved with no long term sequelae. Only 4 of the 50 patients studied prospectively felt that the lidocaine was not a worthwhile treatment, with 32 indicating that it was very worthwhile. NRS pain scores decreased from an average of 9 to 5, and the median duration of any pain relief was 11.5 weeks, ranging from 0 to 36 weeks.

Schafranski [28] reported a series of 23 adult patients treated with daily, increasing infusions of lidocaine increasing from 2 to 5 mg/kg administered over 2 hours. In contrast to the Raphael series, no side effects were observed after any of these doses, and all subjects appeared to have received all five intended doses. Significant improvement in the Visual Analog Pain Scale and in the Fibromyalgia Impact Questionnaire was found and persisted for at least 30 days.

Peri-operative Pain

Systemic infusions of lidocaine have been administered peri-operatively with the intent of decreasing post-operative pain, opioid needs, and ileus. Weibel and colleagues recently provided an updated Cochrane review of this use of lidocaine [29]. Their review included 68 trials with 4525 randomized participants. The analysis was complicated by a multiplicity of surgery types, lidocaine doses and infusion durations. Most lidocaine infusions were in the familiar range of 1–5 mg/kg. Some trials used a bolus at the induction of anesthesia or at first incision, and others started the lidocaine at the end of the surgery. Some infusions did not continue beyond the end of anesthesia, others were maintained from 1 to 24 hours postoperatively [30].

These and other reviewers found the clinical studies of perioperative lidocaine to be generally small and of poor methodologic quality [29, 31]. In cases wherein a decrease in pain or post-operative opioid demand were noted, the magnitude of any benefit was considered clinically non-significant. The average 8 hour reductions in the time to first defecation as a marker of effects on ileus was not considered to be of substantial clinical significance. There was no effect of peri-operative lidocaine on the time to discharge following either outpatient or inpatient surgical procedures.

Sickle Cell Pain

Only one report was found that reported benefit of treating the pain of sickle cell crisis with intravenous lidocaine. Nguyen [32] and colleagues retrospectively identified 11 patients who had received IV lidocaine for pain for a total of 15 courses. Eight of the 15 treatment trials decreased pain scores by at least 20% and reduced

opioid needs by over 30%. Rather than a short infusion (30–60 minutes), these infusions of lidocaine were run over 2–8 days at rates of 0.5–1.9 mg/kg/hour. Two patients experienced reversible confusion and dizziness.

Pediatric Use

The use of systemic lidocaine for the treatment of pain in children is not common, but appears to be safe and similarly effective as in adults. The previously mentioned report of benefit of a prolonged IV lidocaine infusion in an 11 year old boy included titration of rate to a target concentration of 2–5 mg/L with no reported side effects [24]. After demonstrating a response to lidocaine the child was successfully transitioned to an outpatient regimen of oral mexiletine. Massey et al. reported a case of a child with refractory cancer-related pain who was treated with a continuous lidocaine infusion [33]. The infusion of lidocaine initiated at 2.1 mg/kg/min was able to displace a sufentanil infusion of 18 mcg/kg/hour, and was continued at rates up to 3.8 mg/kg/hour after discharge to the patient's home with no significant adverse effects.

Gibbons, et al., reported four cases of children with severe, opioid-refractory pain who responded to prolonged IV lidocaine infusions that averaged 2.2 days in length and ranged from 5 hours to 17 days [34]. Lidocaine infusions were started at a rate of 1.8 mg/kg/hour and adverse effects were mild and reversible. As is described by others, the relief from pain was greatest in those patients who had the most severe pain prior to the treatment, and relief was durable for weeks to months.

In a recent review, Lauder reported on the experience of using intravenous and subcutaneous lidocaine in children suffering from chronic pain [3]. Of the 45 children considered appropriate for a trial of intravenous lidocaine (73% with neuropathic pain or CRPS), 73% had a significant reduction in pain and improvement in function. The response of different types of pain to lidocaine was not described, but the children tolerated the escalating infusions well.

Emergency Department Use

Silva and colleagues performed a systematic review of reports of the use of lidocaine in the Emergency Department [35]. In general, most studies were small, inconsistent in their reporting of doses and of rescue doses of opioids or nonsteroidal anti-inflammatories (NSAIDs), and unblinded. Of the 61 articles meriting close examination, only 6 were considered sufficiently randomized and blinded to provide insight into the utility of IV lidocaine for severe pain. Their review and others suggests that lidocaine was not better than placebo for the treatment of migraine headaches [35, 36]. IV lidocaine was found to have good analgesic benefit in patients with renal colic or critical limb ischemia, equaling or exceeding the benefit of opiates or ketorolac. A separate Cochrane review found equivalent benefit of opioids and NSAIDs for renal colic [37]. The Silva review suggests that IV lidocaine can be considered as first line analgesia in such patients who may have a

relative or absolute contraindication to receive opioids or NSAIDs, but larger, well-controlled studies are needed to support this premise.

Subcutaneous Infusion

The use of extended subcutaneous infusions of lidocaine have been reported in several case series [22, 38, 39]. The limited number of published case series have, in some instances, utilized an intravenous bolus to demonstrate benefit of the lidocaine, followed by a subcutaneous infusion to simplify outpatient treatment with the drug. The use of subcutaneous infusions provides the convenience and safety of avoiding the need for a permanent venous catheter or changing peripheral venous catheters.

The rate of subcutaneous infusion is the same as for intravenous infusions, typically starting at 100 mg/hr. The 10% w/v lidocaine concentration in the infusate for subcutaneous infusions is higher than that used for intravenous infusions to minimize the volume required for drug delivery. This higher lidocaine concentration poses a risk if the bag intended for subcutaneous infusion is mistakenly infused intravenously at flow rates appropriate for the typical IV infusion concentrations of 0.8% (2 gm lidocaine in 250 mL). Preservative-free lidocaine must be used for both intravenous and subcutaneous infusions.

Durations of subcutaneous infusions have varied from days to weeks, and even months. The infusions are generally well tolerated, with the nature and incidence of adverse effects similar to that of intravenous infusions. Once discontinued, the duration of benefit of the prolonged lidocaine infusion upon improved analgesia can be very durable [22, 39].

Contraindications

Lidocaine is contraindicated in FDA-approved labeling in patients with a known hypersensitivity to amide-type local anesthetics. A 12-lead electrocardiogram (ECG) is usually performed to rule out abnormal conduction pathways prior to the first administration of an intravenous infusion of lidocaine for the purpose of treating neuropathic pain. Although not formalized, the use of intravenous lidocaine should be avoided in patients for whom administration of mexiletine or flecanide is contraindicated. These drugs are contraindicated in patients in whom an ECG demonstrates pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block) unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur [6]. Continuous cardiac telemetry is not a standard of care for lidocaine infusions for the treatment of pain [40, 41].

Formulations of lidocaine containing epinephrine must not be administered by IM or intravenous injection and are intended only for local anesthesia. Similarly,

only preservative-free formulations of lidocaine can be used for systemic administration.

Hepatic impairment and heart failure can be expected to decrease the clearance of lidocaine to its metabolites. The decrease in elimination rate is reported to be as much as 40% [42]. This decrease in clearance does not prohibit the use of lidocaine, but if extended infusions are intended beyond 60 minutes the initial infusion rate should be decreased and then escalated based upon combined plasma concentrations of lidocaine and MEGX.

Side Effects

Acute adverse events with systemic lidocaine infusions for the treatment of neuropathic pain or hyperalgesia are common and concentration dependent [43–45]. Commonly the initial side effects are peri-oral numbness, altered taste, and slurring of speech. Mental confusion can occur, and if concentrations are sufficiently high, cardiac arrhythmias, hypotension, loss of consciousness and even seizures may be precipitated. Fortunately, such severe effects are uncommon in patients treated with systemic lidocaine for pain and resolve with supportive care [46].

The anti-arrhythmic, systemic analgesic, and adverse effects of systemic lidocaine are considered to be related to the concentration of lidocaine and of its metabolites. The rate of lidocaine infusion (e.g., delivery of the same dose over 30 minutes vs 60 minutes) is therefore expected to affect the incidence of side effects. This is illustrated in Fig. 1.1 comparing the effect of infusing a 500 dose of lidocaine over 30 minutes (blue, dashed line) instead of 60 minutes (solid orange line).

Using published pharmacokinetic parameters to estimate the concentration time curve [47], the initial, rapid decline in concentration from the distribution phase of

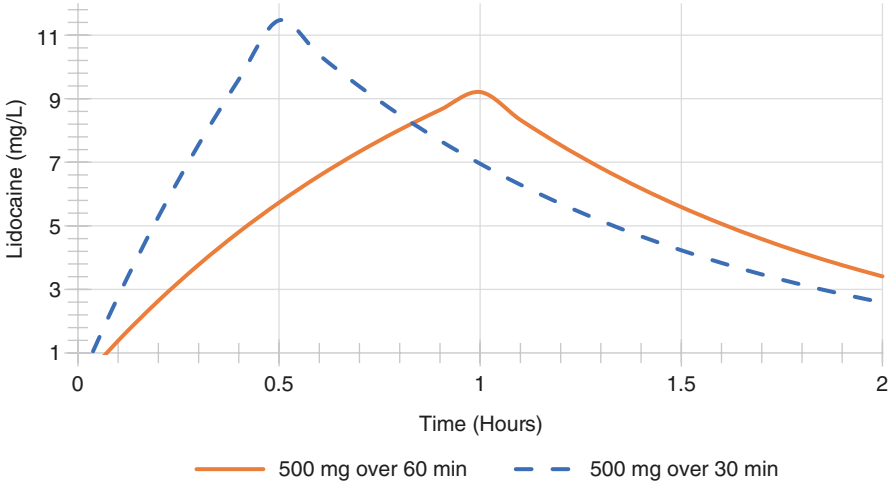

Fig. 1.1 Effect of increasing duration of infusion on peak lidocaine concentration

lidocaine is noticeable for both infusion times. The peak concentration of lidocaine is lower with longer infusions because the slower infusion rate permits both more metabolism and distribution of the drug from plasma to tissue. Decreasing the rate of lidocaine infusion can be expected to reduce the incidence of adverse events, and stopping an infusion that is causing unwanted effects usually leads to prompt dissipation of minor side effects such as confusion and peri-oral numbness. Table 1.1 lists the adverse effects noted in a retrospective chart review of adult patients receiving lidocaine for the treatment of pain at an initial, fixed dose of 500 mg infused over 30 minutes (16.7 mg/min, or approximately 14 mg/kg/hour) [43].

Adverse effects reported in Table 1.1 are given as the percentage of 69 lidocaine-treated patients who experienced each side effect. The starting infusion rate was 16.7 mg/min, and was reduced in patients who experienced adverse effects as this dose. Side effects were reported by the either the patient or the administering nurse. The same patient may be represented multiple times at different infusion rates. The average infusion rate of the infusion that the patient experienced the adverse effect is also reported in mg/min. No ECG monitoring was performed during any infusions [43].

At the onset of symptomatic side effects of lidocaine and its metabolites, the usual policy should be to stop the infusion until the adverse effects dissipate. If the side effects were not serious, the remainder of the lidocaine infusion can be re-started at 50% of the previous rate. If patients demonstrate an analgesic benefit from lidocaine infusions, they may be willing to tolerate some level of dysgeusia and

Table 1.1 Lidocaine side effect incidence

Side effect	Percentage of patients affected	Average infusion rate at which side effect occurred (mg/min)
Total	79.7	13.1
Lightheadedness	44.9	14.5
Other	39.1	14.4
Dizziness/vertigo	30.4	13.0
Peri-oral numbness	23.2	13.7
Speech disturbance	23.1	15.3
Clumsiness/ incoordination	18.8	11.1
Nausea/vomiting	15.9	11.6
Sedation/lethargy	13.0	13.4
Headache	8.7	13.5
Peripheral numbness/ dysesthesias	8.7	13.4
Tinnitus	5.8	16.7
Confusion	2.9	12.8
Tingling	2.9	16.7
Delirium	1.4	11.7
Metallic taste	1.4	16.7
Muscle twitching	1.4	7.8
Arrhythmia	0	N/A

peri-oral numbness in later infusions, but ideally a rate can be found that provides analgesic benefit without bothersome side effects.

Serious events such as seizures, coma, and/or cardiac arrhythmia and collapse have been described with lidocaine infusions or by local infiltration. These are typically idiosyncratic events, or the result of excessive doses. Seizures are rare and are usually preceded by more common prodromal signs and symptoms, yet 20% of patients experiencing a seizure associated with lidocaine did not demonstrate a prodrome [46]. Airway support and oxygenation must be assured if a seizure occurs. Seizures can be treated with a benzodiazepine such as lorazepam, since the use of benzodiazepines are not expected to affect the risk of cardiac arrhythmias. In cases of cardiovascular collapse, the intravenous administration of small (10–100 mcg) boluses of epinephrine are preferred to a larger bolus. Vasopressin and calcium channel blockers are not recommended [46].

Intravenous infusion of 20% lipid emulsion is recommended in cases of severe lidocaine toxicity [46]. The lipid emulsion is presumed to sequester the lidocaine in the lipid emulsion, removing it from the aqueous plasma phase. The ASRA guidelines recommend an IV bolus of 1.5 ml/kg of 20% lipid emulsion, followed by an infusion of 0.25 ml/kg/min for at least 10 minutes after the return of cardiovascular stability. It is obvious that in such instances the infusion of lidocaine should be halted. The administration of subsequent doses of lidocaine after resolution of the adverse effects should only be allowed if the patient showed substantial analgesic benefit, and if the reason for the adverse event can be adequately explained and subsequently avoided.

Monitoring

In addition to inquiring about adverse events arising from prior exposure to lidocaine or other amide anesthetics, a 12-lead ECG should be performed before deciding to implement an intravenous infusion of lidocaine. The presence of second- or third-degree conduction defects or right bundle branch block are usually contraindications for lidocaine infusions. The administration of lidocaine in such patients with continuous, monitored cardiac telemetry may be an option, but the literature to date does not provide a useful guide to the safety and utility of lidocaine infusions for pain in these higher risk patients. Although continuous cardiac telemetry is likely performed at some sites infusing lidocaine and is considered “essential” in the FDA-approved labeling of its use as an anti-arrhythmic [6], it is not a routine component in most reports of lidocaine for neuropathic pain [6, 7]. A physician or other qualified health care professional should be immediately available to diagnose and treat serious adverse events arising from lidocaine infusions regardless of whether telemetry is used.

The timing of blood sampling for lidocaine concentrations is problematic in that such patients are commonly treated as outpatients. There is an eagerness on the part of the patient to depart the infusion center after the completion of a short infusion, and for the facility to cycle the chair for the next patient. As can be seen in Fig. 1.1, there is a rapid decrease in the concentration of lidocaine after the conclusion of the

infusion. Inconsistency in the timing of blood samples after the end of the infusion will therefore lead to dramatically different drug concentrations. Waiting for 1 hour to allow distribution of the drug to the tissue compartment should result in more reproducible results, but may not reflect the utility of the dose as manifested by the peak concentration of the infusion. It is also much more inconvenient for the patient who is asked to stay for a blood sample. Blood sampling just prior to the end of the infusion or collected during the infusion after the onset of adverse events may be informative, but if possible, should be collected from the arm opposite the lidocaine infusion. Blood samples collected from the same IV catheter and tubing as was used for the infusion itself are likely to yield inappropriately high drug concentrations due to the desorption of drug from the tubing.

Lidocaine concentrations of at least 1–2 mg/L are considered necessary for the anti-arrhythmic effect of the drug, and concentrations of at least 5 mg/L have been reported to be needed to control arrhythmias. Lidocaine and MEGX concentrations are not routinely obtained during short infusions of lidocaine for the treatment of neuropathic pain, and no systematically-collected concentrations of both lidocaine and MEGX have been reported for the treatment of neuropathic pain. Modification of the lidocaine infusion rate based upon drug concentrations is impractical when administered as a 30–60 minute intermittent infusion but may be useful in assuring an adequate therapeutic trial and minimizing adverse effects during a more prolonged infusion. Blood sampling to obtain lidocaine and MEGX concentrations may be useful in patients experiencing unusual adverse effects, but usually adverse events are empirically addressed by a decrease in the infusion rate of their subsequent doses of lidocaine. Conversely, blood samples for lidocaine and MEGX concentrations may be helpful in determining whether an unsuccessful treatment with lidocaine for neuropathic pain failed because the usual, empiric dose yielded atypically low concentrations in a given individual. Many clinical laboratories will report both lidocaine and MEGX concentrations, since both are considered roughly equivalent in their inhibition of the voltage-gated sodium channel. Although they may play an active role in the analgesic effects of lidocaine infusions, assays of the GX and EG metabolites of lidocaine are not typically available.

Lidocaine and MEGX are bound to alpha-1-acid glycoprotein (AAG), a heat-shock protein that can demonstrate substantial variation in concentration after burns, trauma, surgery, and other acute events [48]. Higher concentrations of AAG lead to higher total concentrations of lidocaine and MEGX, yet the unbound, active concentrations may not vary substantially with AAG concentration. High AAG concentrations and associated higher plasma lidocaine and MEGX concentrations may be misinterpreted and lead to inappropriate reduction in lidocaine infusion rates. Furthermore, the relative contribution of lidocaine, MEGX, EG, and GX for the treatment of neuropathic pain has not been described.

Inhibition of the metabolism of lidocaine can arise from interactions with various drugs and by decreased hepatic blood flow. Patients with heart failure or severe hepatic cirrhosis can be expected to have a slower clearance of lidocaine to its metabolites [8]. Similarly, propranolol and other drugs that decrease cardiac output have been shown to decrease lidocaine clearance [49]. Drugs such as fluvoxamine