

How to Initiate and Monitor Infusional Lidocaine for Severe and/or Neuropathic Pain

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Case Report

The patient, a 51-year-old woman diagnosed with primitive neuroectodermal tumor (peripheral neuroendothelioma) 4 years prior, presented with severe (10/10) unrelenting neuropathic pain due to T6-T8 spinal-cord compression. Increasing doses of intravenous (IV) morphine up to 50 mg/h with frequent 25-mg boluses of morphine provided inadequate relief. Adjuvant analgesics, including gabapentin, baclofen, amitriptyline, clonidine, and clonazepam, provided little relief or caused significant side effects.

Because of the significant pain and lack of response to standard therapies for neuropathic pain, the decision was made to begin a trial of parenteral lidocaine. Treatment with 100 mg of lidocaine IV (approximately 1.5 mg/kg) over 20 minutes produced a rapid decrease in pain intensity over the course of the infusion. Because the trial was successful, a lidocaine infusion was

continued at 100 mg/h. Attempts to reduce the lidocaine infusion rate resulted in increased pain.

As this was a new therapy, we attempted a variety of delivery strategies. Continuous subcutaneous, continuous IV, IV bolus only, or a combination of continuous and bolus lidocaine were tried. The patient reported highest satisfaction with a continuous IV infusion accompanied by bolus doses as needed. As her pain was now better controlled, she was discharged home with hospice care after more than 3 months' hospitalization.

Ongoing clinical monitoring and frequent dosage adjustments continued in the home setting. On average, adequate pain control was maintained with a lidocaine infusion rate of 10–15 mg/h with a 25-mg bolus of lidocaine every 5 minutes for pain exacerbations. Four months after discharge, she died suddenly after development of superior vena cava syndrome [1].

Severe, intractable cancer pain is often due to neuropathic pain syndromes. Neuropathic pain can develop when nerves are injured, compressed, infiltrated, or affected by toxins, as commonly occurs in malignancies, as well as in HIV, diabetes, and other comorbidities common in people with cancer. Although opioids and adjuvant analgesics can be effective in most of these patients, a few individuals will continue to experience unmanageable pain. Novel techniques, such as parenteral lidocaine administration, are beginning to be used in the management of severe neuropathic pain.

Pathophysiology of Neuropathic Pain

To understand the rationale for using parenteral lidocaine, one must appreciate the underlying mechanism of neuropathic pain syndromes. However, because neuropathic pain syndromes represent a diverse group of conditions, one single mechanism cannot explain the underlying pathology. Changes can occur within the peripheral, central, and autonomic nervous system, and multiple

mechanisms are likely involved. Within the peripheral nervous system, changes include abnormal nociceptor (small fiber neurons transmitting noxious stimuli) sensitization and ectopic impulse generation, leading to spontaneous discharge [2, 3]. The neuron becomes more sensitive to any stimulation, resulting in spontaneous pain and hyperalgesia (normally mild painful stimuli, such as a pin prick, are perceived as extremely painful).

Another hypothesized peripheral mechanism includes the development of ephaptic conduction between sensory neurons, where electrical currents in one neuron excite impulse activity in nearby neurons. Furthermore, neuropeptides, such as the cytokine tumor necrosis factor- α , are released in response to inflammation. These cytokines are believed to generate spontaneous ectopic activa-

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tion of nociceptors [4]. Since conduction within neurons is mediated in part by changes in ion concentrations across the membrane, agents that block Na⁺ channels, such as the local anesthetics, are often used to relieve pain [5].

Sodium channel blocking agents, including systemic local anesthetics such as lidocaine, have long been used to treat acute pain and, more recently, chronic pain [6–9]. At subanesthetic doses, lidocaine blocks neuronal function in active or depolarized neurons without interfering with the normal function of other sensory or motor neurons [10]. Historically, outside of its use for procedural pain, parenteral lidocaine has been used as a “challenge” to elucidate whether the patient has neuropathic pain and to ascertain whether adjuvant therapy using oral analogs of lidocaine, such as mexiletine, might be effective. Several open label trials report the benefit of short-term intravenous (IV) lidocaine infusions, lasting 45 minutes to 1 hour, in a variety of neuropathic pain states, including postherpetic and diabetic neuropathy [9, 11, 12]. Anecdotal reports suggest that some patients obtain sustained relief, although many patients report that the pain returns hours or days after the infusion is discontinued.

Based upon these experiences, and the prevalence of severe neuropathic pain in our hospice, we explored the prolonged use of IV or subcutaneous (SC) lidocaine infusions to treat both neuropathic and mixed (neuropathic and nociceptive) pain syndromes.

Initial Experience

While working at an inpatient hospice in 1996, one of us (R.F.) began treating patients suffering from severe neuropathic pain with parenteral lidocaine infusions. At first, we regarded lidocaine as too dangerous for use except by anesthesiologists. Therefore, we investigated lidocaine therapy only in the most difficult-to-treat pain states, restricting its use to only those patients who were closest to death and who might be willing to accept the risk of this “unconventional and possibly dangerous therapy” (as we explained it). However, as our team developed more experience, we came to see lidocaine’s effectiveness, both in controlling patients’ pain and improving their quality of life. Furthermore, despite our fears, we observed little toxicity as an effect of this drug. We have found parenteral lidocaine to be effective in those with chronic neuropathic pain, particularly when

it was associated with malignancy, as well as for severe pain of other etiologies. We have now treated over 100 patients using this technique, some for weeks or months, and have identified advantages to this therapy, as well as characterized those patients who might benefit most from it.

Advantages of Lidocaine Therapy

Lidocaine is inexpensive and effective. Adverse effects of sedation, confusion, nausea, and constipation that accompany the use of opioids and other analgesics, tend to occur less frequently with lidocaine therapy. The side-effect profile of parenteral lidocaine delivered by infusion is predictable and has a wide safety margin [4]. Thanks to its short half-life, the symptoms of lidocaine toxicity are transient and easily reversible by lowering the infusion rate.

Who Might Benefit From Lidocaine Infusion Therapy?

Parenteral lidocaine has been reported to be effective in small studies of various neuropathic pain conditions, including diabetic neuropathy, postoperative pain, post-herpetic neuralgia, centrally mediated pain, headache, and malignant nerve infiltration [13–20]. Based upon the experience of R.F. with more than 100 patients, many or all of whom were also receiving opioids, infusional lidocaine is effective when treating visceral or central pain. Parenteral lidocaine may also be useful when opioids are ineffective or causing unacceptable adverse effects.

PRE-INFUSION ASSESSMENT

To determine whether the patient is a candidate for parenteral lidocaine infusion, a thorough pain assessment is critical. Patients should undergo a complete pain history, quantitative pain assessment, and physical examination. Prior adjuvant therapy and allergies to “caine” anesthetics must be elicited. The presence of heart failure or liver disease, which would increase the toxicity of lidocaine, must be ascertained. A complete medication history is essential, as adjuvant therapies and other, less-invasive modalities are warranted prior to beginning parenteral lidocaine.

LIDOCAINE CHALLENGE

The purpose of a lidocaine challenge is to assess whether an individual patient’s pain is responsive to lidocaine and whether the patient can tolerate the medication. The dosage for testing purposes is

generally 1–3 mg/kg (100 mg is often used) administered IV in a concentration of 8 mg/mL over 20–30 minutes. During the bolus infusion, careful clinical observations of vital signs and pain intensity are conducted at least every 15 minutes. If SC administration is preferred, the initial loading dose is administered over a longer period (30 minutes to 1 hour), and response is generally delayed. If SC infusion is elected, lidocaine is easily concentrated at 40 mg/mL, allowing a 2–3 cc initial dose and hourly infusion rate of 2–3 cc/h. If ineffective, the lidocaine challenge is discontinued and other pain relief modalities must be selected. If effective, an infusion is started.

Lidocaine Infusions

If the lidocaine challenge is effective or partially effective, the patient is started on a continuous infusion, either SC or IV, at 0.5–2 mg/kg per hour, using the lowest possible dose that controls the pain (Table 1). Although lidocaine is generally given as a continuous infusion for pain, we have also tried a patient-controlled analgesia (PCA) format in which the patient could self-administer bolus doses in some cases of intermittent, severe pain.

Lidocaine infusions may reduce pain dramatically or subtly. Occasionally, during the initial in-

fusion, patients will report dramatic stepwise “erasing” of their pain. In other cases, however, patients might say the pain is still severe (rating it a “10” on a scale of 0 to 10) but more “bearable.” Another indication that lidocaine is effective is an improvement in the patient’s functional status (eg, a patient who could not walk due to pain begins to walk) or a reduction in opioid use. Or patients may say, “I don’t feel it working,” but when the rate of infusion is reduced, the pain returns and they notice its previous effectiveness.

TITRATING LIDOCAINE INFUSIONS

As with any therapy, the ideal is to use the lowest effective dose of medication to treat the patient. The usual method of establishing the lowest effective dose is to reduce the dose of lidocaine gradually until pain returns. Doses above 2 mg/kg per hour are rarely indicated. This experience with parenteral lidocaine mirrors that of Wallace and colleagues [8], who reported a lidocaine dose-response curve for pain relief characterized by a clearly defined breakpoint in dosage, below which pain persisted and at or above which pain was dramatically reduced. Although doses may be reduced among those with hepatic or cardiac disease, these conditions are not contraindications in the case of severe neuropathic pain.

TOXICITY

Lidocaine infusions to manage pain are generally in the range of 1–2 mg/kg per hour. At this rate, blood levels are often less than 3 µg/mL and toxicity rarely develops. If blood levels increase, the side effects are sequential, relatively predictable, and easily reversed by stopping or slowing the infusion [4]. At blood levels of 4–6 µg/mL, patients may complain of lightheadedness, numbness around the tongue or mouth, and/or dizziness. They may note a metallic taste in their mouths or experience an increase in blood pressure. The infusion should be slowed or stopped if any one of these events occurs. Although we initially drew blood to measure plasma levels of lidocaine when using this drug for analgesia, this level of monitoring does not seem to be necessary in a palliative care population, nor do most patients want venipuncture.

Plasma concentrations of lidocaine rarely, if ever, exceed these levels when infusions are used for pain. To provide a reference for lidocaine effects at higher plasma levels, at approximately 8 µg/mL, patients can experience visual or auditory distur-

Table 1
When Lidocaine Challenge Works,
What Next?

OVER THE NEXT 72 HOURS:

- Gradually titrate downward to try to determine the lowest possible effective dose of lidocaine.
- Monitor for any signs of toxicity, particularly after dosage increases.
- Reduce opioids rapidly if patient demonstrates signs/symptoms of toxicity (particularly sedation).
- If pain is exclusively intermittent, initiate a trial of bolus administration.
- If the patient did not receive an adequate trial of adjuvant analgesics, sequentially try adjuvant therapy and titrate the dose upward until analgesia or adverse effects occur.
- Discuss signs and symptoms of possible toxicity with patients and families.
- Assess the competency of the caregiving situation if unable to wean the patient off lidocaine and he or she wishes to return home.
- If lidocaine infusion continues to be indicated:
 - Consider invasive therapies, such as epidural nerve blocks.
 - Consider home infusion.



PATIENT INFORMATION SHEET

Lidocaine Infusion

Lidocaine

Your doctor has prescribed lidocaine to treat your pain. Lidocaine is a local anesthetic similar to the anesthetic dentists use to numb your tooth when you get a filling. It seems to work by quieting nerves, which are firing when they shouldn't be, thereby reducing your pain.

Lidocaine belongs to an entirely different family from morphine and can be extremely effective at reducing certain kinds of pain. Lidocaine is administered either intravenously (in the vein) or subcutaneously (under the skin) by a portable pump. The pump delivers this medication as a continuous infusion, delivering the same amount every hour for 24 hours a day. In some cases, your pump may allow you to receive extra doses, called bolus doses, which you can give to yourself if the pain returns.

Side Effects of Lidocaine

Lidocaine is a relatively safe drug when given in low doses. However, even at low doses, certain side effects can occur. The most serious side effect is an allergic reaction to the medication, which can produce sudden, severe difficulty in breathing. The allergic reaction also can increase the chances of having an irregular heartbeat, which, in rare cases, can lead to sudden death. Although allergic reactions to lidocaine are serious, they are fortunately rare.

The most common side effects you might experience are usually related to having too much of the drug in your body. When this happens, you may experience numbness around your mouth, dizziness, or even a sense of being drunk, perhaps with slurring of speech.

You also may experience hallucinations, muscle twitches, or even a sense of being detached from your body. Though these side effects go away very quickly, once the infusion is stopped or lowered and blood levels of lidocaine drop, they should prompt a call to your nurse.

In rare cases, lidocaine can produce seizures, usually when the dose being given is too high. In these cases, the infusion should be stopped, the nurse called, and seizure medication given.

Sometimes, you may experience problems in the area where the lidocaine enters the body. If the medication is given under the skin, you and the nurse should check for redness, soreness, or hardening of the site. These signs indicate that the site should be changed. In general, the site should be changed every 3 days. However, if redness develops, the site of entry may have to be changed more frequently.

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You are welcome to photocopy this patient information sheet for your patients.

bances, dissociation, muscle twitching, and decreased blood pressure. At 12 $\mu\text{g/mL}$, convulsions may be noted; at 16 $\mu\text{g/mL}$, coma may ensue, and at levels above 20 $\mu\text{g/mL}$ respiratory arrest and cardiovascular collapse can occur. Thus, at the doses used to provide pain relief, parenteral lidocaine infusions are safe.

Other toxicities include local redness or erythema at the SC infusion site. Changing the site every few days can obviate the local irritation.

Titration Opioids With Lidocaine

Many patients whom we have treated with lidocaine infusions were receiving high doses of parenteral or oral opioids concomitantly. Lidocaine infusions can reduce pain and the need for opioids dramatically. In fact, if opioid dosages are not reduced when pain reduction is achieved through a lidocaine infusion, opioid side effects may develop or worsen.

For example, a previously well-tolerated opioid dose may lead to significant sedation when pain is relieved by infusing lidocaine. Interestingly, we have never seen any sign of opioid withdrawal, despite rapid discontinuation of even high-dose opioid therapy (eg, a reduction from 500 $\mu\text{g/h}$ of SC fentanyl to no opioid use over 24 hours or 90 mg/h of IV hydromorphone titrated to 1–2 mg/h in less than 24 hours).

Adjuvant Therapies

In an ideal world, oral adjuvant therapies would already have been tried prior to instituting a parenteral lidocaine infusion, but some patients may present with severe neuropathic pain without ever having had an adjuvant analgesic. Most adjuvant analgesics must be titrated gradually, delaying pain relief. Ideally, parenteral lidocaine is a time-limited strategy for rapidly treating severe neuropathic pain. Once pain is under control, adjuvant therapy can be instituted and titrated so that the pain can be managed more conveniently, without the need for catheters or infusion pumps.

However, despite a wide variety of adjuvant agents, including antidepressants, anticonvulsants, corticosteroids, and antiarrhythmics, very little information exists regarding which therapies might be most effective in those patients who have responded favorably to lidocaine infusions. The majority of the patients we treated with parenteral lidocaine therapy were successfully transferred to

Table 2**Protocol for Home Infusion**

Determine whether to use: <ul style="list-style-type: none"> • Subcutaneous or intravenous administration. • Bolus doses only, continuous infusions, or a combination of both.
Patient must have a stable caregiver situation, with 24-hour supervision by a competent adult.
Patient must consent to being visited by a registered nurse 2–7 times a week.
Patients should understand that any redness or induration at the site of subcutaneous injection indicates a need to switch to a different site (abdominal and thigh sites are preferable).
Patient should agree to frequent adjustments of lidocaine dosage in an attempt to determine the minimum dose at which patient is comfortable.
Patient/caregiver should have the ability to clearly describe signs and symptoms of lidocaine toxicity and show ability to turn off the pump.
Patient/caregiver should be provided with a lidocaine patient information sheet.
Consider providing benzodiazepine in home for sublingual or subcutaneous administration in the event of seizures.

Infusional Lidocaine

oral agents, most commonly gabapentin. Because few data exist, the clinician must use a trial-and-error approach, sequentially introducing different adjuvant agents and titrating each one until an analgesic or adverse effect occurs. If an adjuvant drug is found to be effective, the lidocaine infusion is gradually reduced and discontinued, if possible. If these attempts fail, patients may be maintained for weeks to months on infusional lidocaine without any adverse effects.

Home Infusion of Lidocaine

If the patient is unable to taper off the lidocaine, refuses or is not a candidate for more invasive therapies, and requires continuous infusion at home for ongoing pain relief and, moreover, strongly desires discharge, home infusion may be considered (Table 2). Lidocaine infusions may be administered at home via an ambulatory pump identical to those used for opioid infusions in a PCA setting. Because they are compatible, lidocaine may be used together with opioid infusions. Another advantage is that lidocaine is inexpensive, with a 24-hour supply costing less than \$5.

Lessons Learned

Lidocaine infusions, used over the short or long term, have become an indispensable part of the armamentarium for treating intractable severe pain, particularly neuropathic pain. Regardless of the setting in which lidocaine will be used, the interdisciplinary team must work together to educate themselves about this approach and develop policies and systems for providing this technique in a safe and timely manner. Finally, this modality deserves further study in the hospice and palliative care setting to determine the appropriate dose, schedule, route, and indications for lidocaine infusions to improve comfort at the end of life.

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