PEDIATRIC PHARMACOTHERAPY

UNIVERSITY of VIRGINIA Children's Hospital

Volume 19 Number 12 December 2013

Use of Lidocaine for Analgesia in Children and Adolescents

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Lidocaine has been used as an anesthetic and analgesic for more than half a century. First synthesized in 1943, the injectable formulation of lidocaine was approved for local and regional anesthesia in the United States on November 19, 1948.[1,2] Since that time, a variety of intravenous, intramuscular, and topical methods for administering lidocaine have been developed. The transdermal lidocaine 5% patch (Lidoderm®) was approved by the Food and Drug Administration on March 19, 1999 for relief of pain associated with post-herpetic neuralgia in adults.[2] Use of the patches has expanded to other chronic pain syndromes and to the management of postoperative pain in children as well as adults.[3] Continuous lidocaine infusions offer another option for providing analgesia.[4] Although not well studied in pediatric patients, this technique has the potential to reduce reliance on opioids and may prove to be a valuable addition to pain management in children.

Mechanism of Action

Lidocaine, 2-(diethylamino)-N-(2,6-dimethyl phenyl)-acetamide, is an amide local anesthetic agent. The amide anesthetics block fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, preventing depolarization and inhibiting the generation and propagation of nerve impulses. At lower blood concentrations, sensory neurons are primarily affected while at higher concentrations the effects become generalized. Lidocaine also possesses anti-inflammatory and immunomodulating properties. In comparison to other agents in the class, lidocaine has a rapid onset of action and an intermediate duration of effect.[1,2]

Pharmacokinetics and Pharmacodynamics

Lidocaine is widely distributed after IV administration, with a volume of distribution in adults of 0.7-2.7 L/kg. It crosses both the placental and blood-brain barriers. At therapeutic concentrations lidocaine is 60-80% protein bound, primarily to alpha-1-acid glycoprotein. A dose or concentration-response relationship for the analgesic effects of lidocaine has not been established, but several investigators have reported efficacy with plasma concentrations less than those needed to control arrhythmias (1.5-5 mcg/mL) and well below the level typically associated with toxicity (6 mcg/mL).[1,2] The concentration of lidocaine achieved in the blood after application of transdermal lidocaine patches depends on both surface area covered and duration of application. In a premarketing study of 15 adults, application of three lidocaine 5% patches (2,100 mg total dose covering a 420 cm^2 area) for a 12-hour period resulted in a maximum plasma concentration of 0.13 $\pm$ 0.06 mcg/mL. When worn for the recommended 12 hours, only 3 $\pm$ 2% of the lidocaine in a patch will be absorbed. Use of the patches for up to three days resulted in no drug accumulation.[1,3] Two additional studies in adults using four patches for up to 24 hours/day resulted in mean plasma concentrations of 0.15-0.22 mcg/mL.[2,6,7]

Lidocaine is rapidly metabolized in the liver, primarily via CYP1A2 and CYP3A4-mediated oxidative N-deethylation to monoethylglycine-xylidide (MEGX), then further metabolized to glycinexylidide (GX). These two compounds are pharmacologically active, but less potent than the parent drug. After IV lidocaine administration, the concentrations of MEGX and GX are approximately 10-40% and 5-10% of the lidocaine concentration achieved, respectively. Both lidocaine and its metabolites are excreted by the kidneys; less than 10% of a dose is excreted in the urine as unchanged drug. The mean systemic clearance in a study of 15 adults was 0.64 $\pm$ 0.18 L/min. The average half-life of lidocaine in adults is 1.5-2 hours; however it may be prolonged in patients receiving lidocaine infusions for periods longer than 24 hours. In adults with hepatic dysfunction, the half-life of lidocaine may reach values more than two-fold greater than in healthy adults. Renal dysfunction may lead to accumulation of MEGX and GX. Lidocaine is not removed by dialysis.[1,2,5]

Clinical Experience

Transdermal Lidocaine 5%

Lidocaine 5% patches block pain impulse generation and transmission in damaged or

dysfunctional nociceptors directly under the site of application. The drug penetrates the skin, soft tissue, and peripheral nerves to produce analgesia without numbness. This dosage formulation allows for targeted application, which has been beneficial for pain near incisions or scars, trigeminal nerve pain, and traumatic injuries such as rib fractures. Response to the patches has been mixed. While most controlled studies have shown benefit, there are papers demonstrating no significant difference in pain scores between the patches and placebo.[3] It has recently been suggested that patients most likely to respond are those with allodynia, hyperalgesia, or continuous pain.[8,9]

Four papers have described the utility of transdermal lidocaine in children.[10-13] The first report, published by Frost in 2003, described use in a 10-year-old girl with complex regional pain syndrome type 1 after arthroscopic surgery for an ankle injury.[10] She experienced significant allodynia and hyperalgesia that prevented her from participating in physical therapy. Acetaminophen, ibuprofen, transcutaneous electrical nerve stimulation, gabapentin, amitriptyline, tramadol, and lumbar sympathetic ganglion nerve blockade provided no benefit. After experiencing partial relief with a spinal cord stimulator, she was given a trial of doxazosin 1 mg daily, zaleplon 5 mg at bedtime, and one lidocaine patch daily. There was improvement within a week, which continued to the point of allowing physical therapy. At the time of publication, she had been using a daily lidocaine patch for over a year.

In 2008, Nayak and Cunliffe described use of the patch in five adolescents with chronic neuropathic scar pain after a burn.[11] The patients ranged in age from 11 to 18 years and had been experiencing pain for 1 to 4 years. The average visual analog scale (VAS) pain score was 8 at initiation. Patients wore 1, 1 ½, or 2 patches for 12 hours per day. Patch administration was being based on the size of the burned area. One patient experienced no relief and the patches were discontinued after a week, while the others continued on therapy for 12 to 16 weeks. VAS scores at 3-month follow-up ranged from 0 to 4. There were no adverse effects reported.

In a 2012 paper, Rasolofo and colleagues found a consistent reduction in pain scores with the use of lidocaine patches in six children (6-18 years of age) with refractory pain associated with sickle cell vaso-occlusive crisis.[12] Based on their success, the authors are currently enrolling children between 6 and 21 years of age into a larger phase 2 open-label study (NCT01314300) to assess the safety and efficacy of transdermal lidocaine for vaso-occlusive sickle cell pain.

Similar efficacy was reported by Silva and colleagues earlier this year in children with neuropathic pain following burn injury.[13] Fourteen patients were enrolled in this observational study. Twelve were included in the final analysis, ranging from 8 to 16 years of age. Patches were cut as needed to completely cover the painful area, and ranged from ⅛ to ½ patch. Mean pain score, using the FACES pain scale, declined from 7 at initiation to 0.2 at 1 month and 0 at 3 months. All patients experienced improved mobility and activity levels, improved sleep, and the ability to touch the area of their original burn without pain. Plasma lidocaine concentrations were collected in all 14 patients. All were well below the range associated with systemic toxicity. The highest concentration obtained was 0.027 mcg/mL.

Lidocaine Infusions

Lidocaine infusions have been used in the management of postoperative and chronic neuropathic pain for more than a decade. A systematic review published in 2010 included 16 randomized controlled trials of lidocaine infusion for postoperative pain. Eight of the trials showed statistically significant improvements in pain scores compared to opioids alone.[4] Half of the papers also demonstrated a reduction in opioid requirements with the addition of lidocaine.

The first paper to describe the use of a lidocaine infusion for analgesia in a child was published in 1997.[14] Wallace and colleagues conducted an open-label study in five children (4-7 years of age) with neuroblastoma who were undergoing immunotherapy with anti-GD_2 antibody given as four daily infusions per month. All children had received morphine for previous immunotherapy and were given either lidocaine or morphine on an alternating basis with each subsequent course. Lidocaine was administered as a 2 mg/kg bolus followed by an infusion of 1 mg/kg/hr, while morphine was given as a 0.1 mg/kg bolus with an infusion of 0.05-0.1 mg/kg/hr for 7 hours on each of the four days of treatment. There were no significant differences in pain scores or the need for supplemental morphine in the two groups. Lidocaine was associated with less nausea and emesis on the first 2 days of treatment and a significant improvement in mobility on day 4. Mean daily lidocaine plasma levels ranged from 0.55 ± 0.17 to 2.3 ± 2.05 mcg/mL.

Subsequent reports have described successful lidocaine use in children with chronic pain. In a case from 2002, a 5-year-old girl with metastatic retinoblastoma and pain refractory to high-dose opioids improved with the addition of a lidocaine infusion of 35-50 mcg/kg/min (2-3 mg/kg/hr).[15] Another case report described a 5-year-old with neuropathic cancer pain that responded to the addition of lidocaine 9-14 mcg/kg/min (0.54-0.84 mg/kg/hr) and ketamine to her fentanyl regimen.[16] In addition, six pediatric patients (ages 9-17 years) were included in an open-label study of 49 patients with refractory complex

regional pain syndrome.[17] There was a significant decrease in allodynia 3 months post-treatment, decreased signs of inflammation, and minimal adverse effects.

Earlier this year, El-Deeb and colleagues published the first pediatric trial to evaluate low-dose lidocaine infusions for postoperative pain.[18] Eighty children (1-6 years of age) undergoing abdominal surgery were enrolled in a randomized double-blind placebo-controlled study. Patients received lidocaine (a bolus of 1.5 mg/kg followed by a 1.5 mg/kg/hr infusion) or saline for up to 6 hours. Plasma cortisol levels were used as a surrogate for distress. The saline group had significantly higher cortisol concentrations ($p = 0.001$) at induction and during recovery. All lidocaine concentrations were less than 4 mcg/mL. Fentanyl requirements were less in the lidocaine group on postoperative day 1 (5.4 ± 2.9 compared to 14.4 ± 2.5 mcg/kg/day) and day 2 (4.1 ± 2.6 compared to 12.6 ± 3.3 mcg/kg/day). Bowel function also returned earlier. Length of hospitalization was significantly shorter with lidocaine (5 ± 2 versus 7 ± 2 days, $p = 0.03$). A second study of lidocaine infusions for postoperative pain in children (NCT01836614) is currently underway.

Contraindications and Warnings

Lidocaine is contraindicated in patients with a known hypersensitivity. Allergic reactions to lidocaine appear to be rare, but cases of angioedema, laryngospasm, bronchospasm, pruritus, urticaria, anaphylactoid reactions, and shock have been reported. There appears to be minimal cross sensitivity to lidocaine in patients allergic to para-aminobenzoic acid derivatives such as procaine, tetracaine, or benzocaine. Lidocaine should not be used as an analgesic in patients with second or third-degree heart block, or severe sinoatrial block without a pacemaker. Lidocaine analgesia should be considered only in patients with stable cardiovascular and hemodynamic parameters.[1,2]

Early symptoms of lidocaine toxicity include central nervous system (CNS) excitation, with nervousness, lightheadedness or dizziness, anxiety, confusion, tinnitus, blurred or double vision, a sensation of heat, cold, or numbness, twitching, tremor, and vomiting. The period of CNS excitation may be brief in some patients, while others may not exhibit this phase and will present with symptoms of CNS depression. Patients may also exhibit tachypnea, tachycardia, fever, and metabolic acidosis. At higher concentrations (> 5 mcg/mL), symptoms may progress to tonic-clonic seizures, blood pressure and heart rate lability, respiratory depression, and cardiovascular collapse. Patients exhibiting early signs of toxicity should have their infusion decreased and a lidocaine level obtained. If symptoms do not resolve, the infusion should be discontinued. In patients with signs of severe toxicity, lidocaine should be discontinued and supportive therapy initiated.

Intravenous lipid emulsion has been shown to be an effective tool for reducing lidocaine concentrations.[19-21] The American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends that lipid emulsion be considered in patients with systemic local anesthetic toxicity following airway management, administration of benzodiazepines for seizures, and control of cardiac arrhythmias. The ASRA guidelines recommend a bolus of 1.5 mL/kg 20% lipid emulsion followed by a 0.25 mL/kg/min infusion with adjustment based on patient response. The mechanism for the beneficial effect of lipid emulsion is not clearly understood. It has been suggested that fat emulsion serves as a "lipid sink" in the systemic circulation, facilitating dissolution of lidocaine into the lipid micelles of the emulsion which are then cleared by the liver. Administration of lipid emulsion also provides free fatty acids to meet the increased metabolic demands occurring as the result of a lidocaine overdose.[1,2,19-21]

Adverse Effects

Transdermal lidocaine patches and low-dose lidocaine infusions are generally well-tolerated. Patients should be monitored for signs of CNS excitation (lightheadedness, dizziness, vision changes, headache, numbness or tingling of the mouth, tremors, or vomiting). After transdermal application, the most commonly reported adverse reactions include dermatitis, erythema, a burning sensation, bruising, petechia, pruritus, vesicle formation, and blistering or exfoliation of the skin. These reactions are typically mild and resolve within hours after patch removal.[1,2]

Drug Interactions

Use of lidocaine in patients with other local anesthetics may increase the risk for systemic toxicity. Administration of lidocaine in patients receiving Class I antiarrhythmic agents may produce additive or synergistic effects on cardiac conduction and is not recommended. Administration of lidocaine and dihydroergotamine may lead to extreme elevations of blood pressure. Lidocaine concentrations may be elevated when given with drugs metabolized by CYP1A2 or CYP3A4, such as amprenavir, atazanavir, dalfopristin, darunavir, delavirdine, etravirine, fosamprenavir, indinavir, lopinavir, nevirapine, quinupristin, ritonavir, saquinavir, and telaprevir. It is also recommended that drugs which impair hepatic blood flow, such as cimetidine and beta-adrenergic blocking agents, not be used in patients receiving continuous lidocaine infusions because of the potential for reduced clearance.[1,2]

Availability

Lidocaine injection is available from multiple manufacturers in 5 mg/mL (0.5%), 10 mg/mL

(1%), 15 mg/mL (1.5%), and 20 mg/mL (2%) concentrations. Both single dose and multiple-dose products are available. Multiple-dose vials may contain a preservative. The 10 mg/mL and 20 mg/mL single-dose vials are typically used to prepare lidocaine infusions. Transdermal 5% lidocaine patches are available as the original product (Lidoderm®) and as a generic product in boxes of 30 patches. Each 10 cm x 14 cm patch contains 700 mg lidocaine in an aqueous base.[1,2]

Dosing Recommendations

At this time, there are no definitive guidelines for the use of transdermal lidocaine 5% patches in children. Case reports describe using ⅛ to two patches for 12 hours per 24-hour period in children 6 years of age and older.[8-13] Patches should only be applied to intact skin and use of external heat sources such as heating pads which may increase absorption is not recommended. Once a patch is removed, it should be folded and discarded in a container inaccessible to children or pets. After use, the patch will still contain more than 600 mg of drug, enough to produce severe toxicity if swallowed or chewed.[2,3]

As with the lidocaine patch, there is limited information available on the use of lidocaine infusions for analgesia in children. In the papers published to date, low-dose infusions have been initiated with a lidocaine bolus of 1 mg/kg followed by an infusion of 0.5-1.5 mg/kg/hr in children as young as 1 year of age.[14,16-18] Higher infusion rates have been used in patients with refractory chronic pain.[15]

Summary

Lidocaine patches and infusions offer a unique mechanism for providing analgesia and may reduce the need for opioid analgesics in children with postoperative pain or chronic pain syndromes. More research is clearly needed to establish optimal dosing strategies for lidocaine in the pediatric population, including dose-ranging, pharmacokinetic and pharmacodynamic studies, as well as larger studies to demonstrate efficacy and safety.

The editors would like to thank Dr. Lyn Wells for serving as our guest editor this month.

References

1. Lidocaine product information, Hospira, Inc., February 2010. Available at: http://www.hospira.com/Images/EN-2421_32-5726_4.pdf (accessed 11/9/13).
2. Lidoderm® product information, Endo Pharmaceuticals, Inc., January 2013. Available at: www.lidoderm.com (accessed 11/4/13).
3. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol 2003;43:111-7.
4. McCarthy GC, Megall SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs 2010;20:1149-63.
5. Wang JS, Backman JT, Taavitsainen P, et al. Involvement of CYP1A2 and CYP3A4 in lidocaine N-deethylation and 3-hydroxylation in humans. Drug Metab Dispos 2000;28:959-65.
6. Gammaitoni AR, Alvarez NA, Galer BS. Evaluation of the safety and tolerability of continuously applied lidocaine patches 5%. Am J Health Sys Pharm 2002;59:2215-20.
7. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. Ann Pharmacother 2002;36;236-40.
8. Madsen CS, Johnsen B, Fuglsang-Frederiksen A, et al. Differential effects of a 5% lidocaine medicated patch in peripheral nerve injury. Muscle Nerve 2013;48;265-71.
9. Kern K, Nalamachu S, Brasseur L, et al. Can treatment success with 5% lidocaine medicated plaster be predicted in cancer pain with neuropathic components or trigeminal neuropathic pain? J Pain Res 2013;6:261-80.
10. Frost SG. Treatment of complex regional pain syndrome type 1 in a pediatric patient using the lidocaine patch 5%: a case report. Curr Ther Res Clin Exp 2003;64:626-9.
11. Naak S, Cunliffe M. Lidocaine 5% patch for localized chronic neuropathic pain in adolescents: report of five cases. Pediatr Anesth 2008;18:554-8.
12. Rasolofo J, Poncelet M, Rousseau V, et al. Analgesic efficacy of topical lidocaine for vaso-occlusive crisis in children with sickle cell disease. Arch de Pediatrie 2013;20:762-7.
13. Silva MO, Yanez V, Hidalgo G, et al. 5% lidocaine medicated plaster use in children with neuropathic pain from burn sequelae. Pain Med 2013;14:422-9.
14. Wallace MS, Lee J, Sorkin L, et al. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma – a report of a series. Anesth Analg 1997;85:794-6.
15. Massey GV, Pedigo S, Dunn NL, et al. Continuous lidocaine infusion for the relief of refractory malignant pain in a terminally ill pediatric cancer patient. J Ped Heme Onc 2002;24:566-8.
16. Kajiume T, Sera Y, Nakanuno R, et al. Continuous intravenous infusion of ketamine and lidocaine as adjuvant analgesics in a 5-year-old patient with neuropathic cancer pain. J Palliat Med 2012;15:719-22.
17. Schwartzxman RJ, Patel M, Grothusen JR, et al. Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome. Pain Med 2009;10:401-12.
18. El-Deeb A, El-Morsy GZ, Ghanem AAA, et a. The effects of intravenous lidocaine infusion on hospital stay after major abdominal pediatric surgery. A randomized double-blinded study. Egypt J Anaesth 2013;29:225-30.
19. Wolfe JW, Butterworth JF. Local anesthetic systemic toxicity: update on mechanisms and treatment. Curr Opin Anesth 2011;94:561-6.
20. Neal JM, Bernards CM, Butterworth JF, et al. ASRA practice advisory on local anesthetic systemic toxicity. Reg Anesth Pain Med 2010;35:152-61.
21. Presley JD, Chyka PA. Intravenous lipid emulsion to reverse acute drug toxicity in pediatric patients. Ann Pharmacother 2013;47:735-43.

Formulary Update

The results of the November/December meeting of the Pharmacy and Therapeutics Committee will be provided in the January 2014 issue.

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/home.html. For comments or suggestions for future issues, please contact us at mlb3u@virginia.edu.