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Lidocaine Toxicity

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Introduction

Lidocaine is a local anesthetic drug that produces transient loss of sensory, motor, and autonomic function when the drug is injected or applied in proximity to neural tissue. It is the most common local anesthetic and used in almost all medical specialties. [1][2]It also is commonly used as an antiarrhythmic agent to depress ventricular arrhythmias. Infusions of lidocaine (and procaine) have been used to supplement general anesthetic techniques, as they are capable of reducing the minimum alveolar concentration of volatile anesthetics by up to 40% as well as providing pain relief in the peri-operative phase. It is in the class of the local amide anesthetics, which, compared to the ester-type local anesthetics, is usually well tolerated with only rare occasions of allergic reactions. Amide local anesthetics are metabolized (N-dealkylation and hydroxylation) by microsomal P-450 enzymes in the liver.

Applied either by injection, inhalation, or as a topical agent to provide anesthesia, lidocaine has a good safety margin before reaching toxic blood levels. Since it can be applied in various forms to the same patients, however, care must be taken to keep track of the total dose given to minimize its systemic toxicity. In addition, one should take into account the dose of any other local anesthetics that may have been administered to the same patient, as toxic doses appear to be additive. Lidocaine toxicity not only is determined by the total dose (usually 4.5 mg/kg) but also by the rate of absorption, which is dependent on the blood flow of that tissue. To reduce blood flow to the injection site and therefore the rate of absorption, vasoconstrictors such as epinephrine 1:200000 is frequently used and may increase the toxic dose to 7 mg/kg.[3][4]

Lidocaine toxicity to muscles and peripheral or neuraxial nerves can occur locally at the site of injection. Transient neurologic symptoms (TNS) after high concentration lidocaine spinal anesthetics have been described multiple times and have led to either reducing the concentration of the dose or switching to a different agent.

In addition to direct nerve toxicity, systemic toxicity affecting the brain and/or cardiac muscle can lead to sudden and dramatic changes in the patient's vital signs.

Finally, there are the side effects of a relative overdose at the site of injection, which can be quite dramatic. Examples include total spinal anesthesia or subdural injection of the drug that can cause severe hemodynamic compromise such as hypotension or bradycardia up to a cardiac and respiratory arrest.

Etiology

Toxicity to local nerves and muscles are thought to be a consequence of the prolonged application of high drug concentrations or the effect of preservatives in the local anesthetic solution or both.[5][6]

Systemic local anesthetic toxicity is due to high systemic plasma levels of lidocaine due to absorption of large doses of lidocaine, which depends mostly on the blood flow at the site of injection: tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > subcutaneous.

Also, blind injection of large volumes into a large muscular area, such as for lumbar plexus block or sciatic nerve blocks, have all of the elements that could lead to systemic lidocaine toxicity.

Spinal anesthetics are very low in total dose and would not cause systemic lidocaine toxicity.

Inadvertent intra-arterial injections may cause local anesthetic toxicity in the tissue beds supplied by that artery even well under the systemic toxic concentration. This complication is seen mostly with injections into the neck, causing central nervous system (CNS) symptoms often during the injection or shortly after that without progressing to the feared cardiac toxicity.

Epidemiology

All sexes are affected equally by lidocaine. Patients who are likely to be more susceptible to local anesthetic toxicity are patients at the extremes of age and women who are pregnant.

Rates of severe systemic toxicity (seizures with or without cardiac arrest) occur on the order of 1:10,000 for epidurals and up to 1:2000 for peripheral nerve blocks, depending on the type of block.

Pathophysiology

Most local anesthetics block voltage-gated sodium channels from inside the cell, preventing subsequent channel activation and interfering with the large transient sodium influx associated with membrane depolarization. Impulse conduction slows, the rate of rising and the magnitude of the action potential decrease, and the threshold for excitation is raised progressively until an action potential can no longer be generated, and impulse propagation is abolished. Hence the pronounced effect of lidocaine toxicity on cells relies on the propagation of action potentials such as the central nervous and the myocardial conduction systems. Local anesthetics also may block calcium and potassium channels and N-methyl-d-aspartate (NMDA) receptors to varying degrees.

Histopathology

All local anesthetics can cause direct neuro-toxicity, depending on the dose and time of contact with the nerve. The occurrence of clinically relevant myopathy and myonecrosis has been described after continuous peripheral blocks, infiltration of wound margins, trigger point injections, and peri- and retrobulbar blocks. Histologically, myofibril hypercontraction progresses to lytic degeneration, edema, and necrosis. Regeneration usually occurs after three to four weeks. Concomitant steroid or epinephrine injections can worsen the myonecrosis.

Toxicokinetics

Potency correlates with lipid solubility, which is the ability of the local anesthetic molecule to penetrate membranes in a hydrophobic environment.

The duration of action also correlates with lipid solubility and protein binding. Highly lipid-soluble and protein-bound local anesthetics have a longer duration of action, presumably because they are less likely to be cleared by blood flow. Local anesthetics that are highly lipid-soluble also exhibit a high degree of plasma protein binding, mostly to alpha-1-acid glycoprotein and, to a lesser extent, albumin; as a direct consequence, their elimination is prolonged. Blood flow to the tissue deposit of local anesthetic determines the absorption rate and is responsible for the plasma level. It will, however, also transport local anesthetics away from the tissue site, reducing the risk of direct nerve toxicity. Lidocaine has a 90% hepatic metabolism, and the elimination half-life is 1.5 to 2 hours, which can be prolonged up to 3.5 fold in patients with the severe liver disease.

History and Physical

The CNS is the site of premonitory signs of overdose in awake patients. Early symptoms are circumoral numbness, tongue paresthesia, and dizziness. Sensory complaints may include tinnitus and blurred vision. Excitatory signs, such as restlessness, agitation, nervousness, or paranoia, may progress to muscle twitches and seizures. Ultimately, with large overdoses, CNS depression, including unconsciousness and coma, can occur. Hypotension and bradycardia can

also be side effects of relative local anesthetic overdoses that sometimes occur during neuraxial blockade or nerve blocks performed near the CNS.

Major cardiovascular toxicity usually requires higher lactic acid (LA) concentration in blood than that which produces seizures. Unintentional intravascular injection of local anesthetics during regional anesthesia produce severe cardiotoxic reactions, including hypotension, atrioventricular heart block, idioventricular rhythms, and life-threatening arrhythmias such as ventricular tachycardia and fibrillation and are usually the presenting signs of local anesthetic toxicity during general anesthesia.

Evaluation

The diagnosis is made clinically. The timing, dose, and site of the lidocaine injection are the main factors in considering systemic manifestations. It is important to keep in mind that even low doses injected inadvertently into an artery going to the brain can cause CNS symptoms.[6][7][8]

For direct local manifestations, such as pain seen in TNS, the concentration, and site of injection will help to make the diagnosis. While imaging the spine with CT or MRI will not help in making the diagnosis of TNS, it will help to rule out other causes that may compress the structures within the spinal canal, which could also cause severe pain after neuraxial blockade and would require urgent surgical decompression. A lidocaine plasma level can be obtained but will take too long for the results to be meaningful for any treatment decisions.

Treatment / Management

Treatment of local anesthetic toxicity is symptomatic by raising the seizure threshold through pharmacologic interventions such as administering benzodiazepines and/or barbiturates or propofol. Hyperventilation with high doses of oxygen reduces cerebral blood flow and also has been used to raise the seizure threshold.[9][10]

The other mainstay of treatment is to reduce the free available local anesthetic concentration in the plasma by administration of lipid emulsions. Due to the high lipid solubility, infusion of lipid emulsions will bind free circulating local anesthetics and lower the plasma levels. The following is the treatment algorithm suggested by the American Society of Regional Anesthesia and Pain Medicine:

"Call for Help"

- Even premonitory CNS systems may progress to severe cardio-respiratory compromise, and many tasks may need to be done simultaneously such as getting code carts and fetching the lipid emulsion.

Initial Focus

- Airway management: ventilate with 100% oxygen

- Seizure suppression: benzodiazepines are preferred; AVOID propofol in patients having signs of cardiovascular instability

Alert the Nearest Facility Having Cardiopulmonary Bypass Capability

Management of Cardiac Arrhythmias

- Basic and Advanced Cardiac Life Support (ACLS) will require adjustment of medications and perhaps prolonged effort
- AVOID vasopressin, calcium channel blockers, beta-blockers, or local anesthetic
- REDUCE individual epinephrine doses to <1 mcg/kg

Lipid Emulsion (20%) Therapy (values in parenthesis are for 70kg patient)

- Bolus 1.5 mL/kg (lean body mass) intravenously over 1 minute (~100mL)
- Continuous infusion 0.25 mL/kg/min (~18 mL/min; adjust by roller clamp)
- Repeat bolus once or twice for persistent cardiovascular collapse
- Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
- Continue infusion for at least 10 minutes after attaining circulatory stability
- Recommended upper limit: Approximately ten mL/kg lipid emulsion over the first 30 minutes"

Resuscitation during LA toxicity may need to include cardiopulmonary bypass, as successful outcomes have been reported even after prolonged resuscitation, which may, in part, be explained by suggestions in animal models that bupivacaine, when added to cardioplegia solution, actually improves function and reduces the cellular damage of rat isolated hearts after prolonged, cold storage.

Differential Diagnosis

The timing of the onset of symptoms related to the injection or application of large doses of lidocaine will most likely make the diagnosis. However, coincidental seizures due to a seizure disorder or panic attacks with hyperventilation may confound the diagnosis.

For direct local toxicity symptoms after lidocaine injection such as radicular pain, first exclude other causes, such as hematoma, that may compress structures in the spinal canal and require urgent surgical decompression. The timing of an epidural abscess in relation to a central neuraxial block would make that diagnosis unlikely. Most epidural abscesses, however, are spontaneous and could potentially coincide with the injection.

Prognosis

The prognosis of lidocaine toxicity depends on the site of manifestation. CNS toxicity is either self-limited or quite amenable to treatment with benzodiazepines, has a good prognosis without sequelae, and does not need further neurologic testing. Cardiac toxicity may require prolonged resuscitation, but the prognosis after return to spontaneous circulation is often very good.

Enhancing Healthcare Team Outcomes

Lidocaine is used by many healthcare professionals including nurse practitioners. Anyone who uses this anesthetic must be aware of its potential toxicity and how to manage it. Because lidocaine can cause seizures and arrhythmias, a neurologist and cardiologist should be consulted immediately. At the same time, the airway should be managed and maintained patent.

The other mainstay of treatment is to reduce the free available local anesthetic concentration in the plasma by administration of lipid emulsions. Due to the high lipid solubility, infusion of lipid emulsions will bind free circulating local anesthetics and lower the plasma levels.

The outcomes of patients with lidocaine toxicity depend on the dose and presence of neurological symptoms. When treatment is prompt, the outcomes are good but any delay in treatment can lead to death.[11][12]

Questions

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