Toxicity of Local Anesthetics

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Most episodes of local anesthetic toxicity result from high blood levels of local anesthetic caused by either accidental intravascular injection or increased uptake from perivascular areas, such as the epidural space or axillary sheath.

Prevention and treatment of local anesthetic toxicity is dependent on the injection of an appropriate volume and concentration of local anesthetic, knowledge of the pharmacologic properties of these drugs, and increased vigilance for the early detection of toxic reactions.

Factors Influencing Blood Levels of Local Anesthetic

The site of injection, choice of drug, dose of local anesthetic, addition of vasoconstrictors, and metabolism determine blood levels of local anesthetic.

Site of Injection. Absorption of local anesthetic is dependent on the blood supply at the site of injection. High perfusion favors high uptake and blood levels. In general, the blood levels after various nerve blocks are:
Intercostal > Caudal > Epidural > Brachial > Plexus > Sciatic > Spinal.

Choice of Local Anesthetic. Local anesthetics with a high degree of tissue binding (etidocaine and bupivacaine) or a large volume of distribution (prilocaine) will have lower blood levels.

Dose of Local Anesthetic. The relationship between total dose of local anesthetic and peak plasma concentration is linear.

Addition of Vasoconstrictors. The actual effect of the addition of epinephrine or phenylephrine is dependent on the sensitivity of the vasculature at the injection site and also the vasoconstrictive or dilating properties of the specific local anesthetic. In general, the addition of vasoconstrictors lowers the peak blood level and increases the time to peak blood level of local anesthetics.

Metabolism. Because little metabolism of local anesthetics occurs at the site of injection, absorption and delivery to the site of metabolism (for amides, the liver; for esters, the plasma) is necessary for local anesthetic metabolism to occur.

Systemic Toxicity

Most toxic reactions to local anesthetics involve the central nervous system (CNS). Severe reactions also involving the cardiovascular system are less frequent, but more difficult to treat.

Central Nervous System Toxicity. CNS toxicity is proportional to local anesthetic potency. More potent, longer-acting drugs tend to be more toxic.

The signs and symptoms of lidocaine-induced CNS toxicity are shown in Fig.1 Initial symptoms are excitatory, resulting from a selective blockade of the inhibitory pathways. Eventual CNS depression and collapse develop as blood levels increase.
The convulsive threshold is decreased by 50% in the presence of hypercarbia. An increase in Paco2 increases cerebral blood flow, and a decrease in pH results in decreased protein binding (more free drug is available).

Cardiovascular System Toxicity. All local anesthetics cause a dose-dependent depression in myocardial contractility and also exhibit vasodilating properties (with the

exception of cocaine, a vasoconstrictor).

Myocardial depression is proportional to local an- Bupivacaine has also been associated with ventricular dysrhythmias, perhaps due to unidirectional conduction blockade resulting in a reentrant pathway.

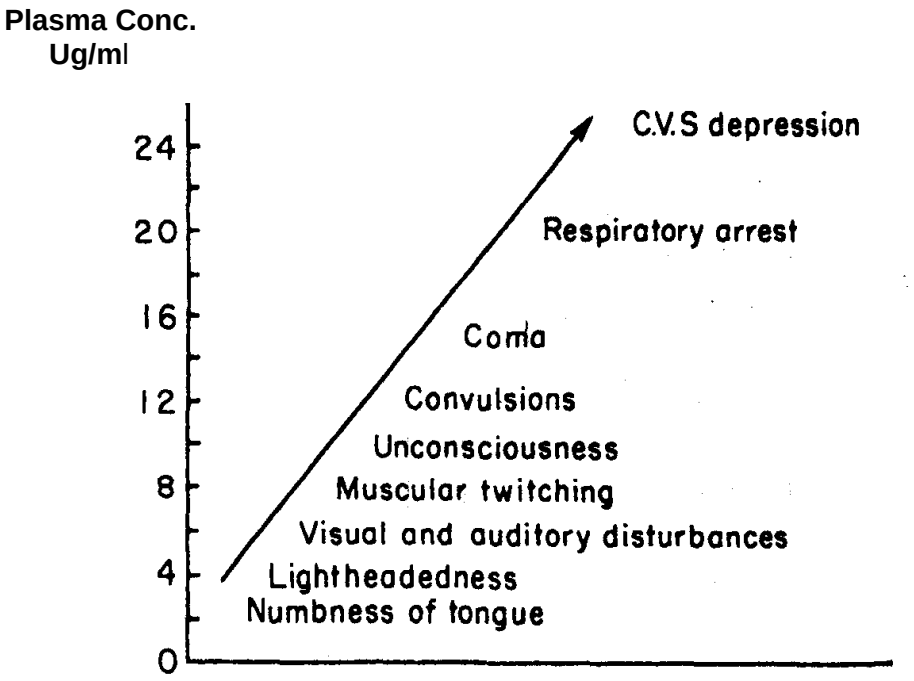

Figure 1:.Relationship of signs and symptoms of local anesthetic toxicity to plasma concentration of lidocaine. CVS, cardiovascular system esthetic potency.

Allergy to Local Anesthetics

True allergies to amide local anesthetics are extremely rare. Metabolism of ester local anesthetics yields para-aminobenzoic acid (PABA), which is a known allergen. A patient who is allergic to PABA should be assumed to be allergic to ester local anesthetics. Methylparaben, a preservative in both ester and amide local anesthetic solutions, is also metabolized to PABA and may cause allergic reactions.

Neural Toxicity

Chioroprocaine has been implicated in the prolonged sensory and motor deficits of at least nine patients. When these reactions occurred, available preparations of chloroprocaine contained 0.2% sodium bisulfite and had a pH of 3.0. Studies have shown that although chloroprocaine itself is not neurotoxic, large amounts of chloroprocaine in the presence of sodium bisulfite and a low pH may cause neurotoxicity. Lidocaine and other local anesthetics also may cause neurotoxicity when administered in high concentrations.

Methemoglobinemia

Methemoglobin may be formed after administration of large doses of prilocaine. In general, doses of about 600 mg are required before clinically significant methemoglobinemia occurs. Usual clinical effects are mild but may be of greater importance in patients with cardiac or respiratory compromise. Methemoglobinemia may be treated by intravenous administration of methylene blue.

Diagnosis, Prevention, and Treatment of Toxic Reactions

Most toxic reactions to local anesthetics can be prevented through safe performance of neural blockade, including careful selection of local anesthetic dose and concentration. Use of a test-dose and incremental injections with intermittent

aspiration decrease the risk of systemic toxicity during epidural anesthesia. Patients should be closely monitored for signs of intravascular injection (i.e., increased blood pressure and heart rate in the presence of epinephrine) or signs of CNS toxicity... The judicious use of a benzodiazepine will raise the seizure threshold.

Treatment of local anesthetic toxic reactions is similar to the management of other medical emergencies, focusing on ensuring adequate airway, breathing, and circulation. An airway should be established and 100% oxygen administered. Hypoxia and hypercarbia must be avoided. If convulsions occur, a small amount of a short-acting barbiturate (thiopental 50 to 100 mg) will rapidly terminate the seizure without causing cardiovascular compromise. Should intubation be required to secure the airway, succinylcholine may be administered. Although the tonic-clonic motions are inhibited in a patient given a neuromuscular relaxant, seizure activity may still be present electroencephalographically.

Most toxic reactions are limited to the CNS. Cardiovascular collapse with refractory ventricular fibrillation may occur, especially with bupivacaine. Sustained cardiopulmonary resuscitation and repeated cardioversion may be necessary. High doses of epinephrine are often required for circulatory support. Ventricular dysrhythmias should be treated with bretylium instead of lidocaine.

Cauda Equina Syndrome

Prolonged neurologic injury with pain, motor paralysis, and sensory changes is a rare complication of spinal anesthesia. Although preservatives or other contaminants administered with the drug have been cited as the cause of this complication in rare reports, neural toxicity has been described following injection of high concentrations and doses of certain local anesthetics, including chloroprocaine and lidocaine. A number of cases were reported in the 1990s after the use of microcatheters for continuous spinal anesthesia with high-dose lidocaine, presumably because this catheter placement allowed a high concentration of the drug to “streamline” and accumulate near sacral nerve roots.

Transient Neurologic

Pollock and others have described a significant incidence (10% to 30%) of transient neurologic symptoms (TNS) after spinal anesthesia with normal doses of lidocaine. Severe pain radiating down both legs is the most commonly described symptom. Associated factors include surgical position (specifically lithotomy), early ambulation, and obesity. This poses a special problem when spinal anesthesia is chosen for short procedures, because there are few alternatives for outpatient regional anesthesia. Alternatives to lidocaine include procaine, mepivacaine (which has, also been associated with TNS), very-low-dose lidoaine (25 mg) with fentanyl (25 mg), and very-low-dose bupivacaine (4 to 7 mg) with fentanyl (10 to 25 mg).

Selected References

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