

# Local anesthetic toxicosis

by

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A wide variety of local anesthetic formulations provide local, regional, and spinal anesthesia during diagnostic and surgical procedures and are used to treat cardiac arrhythmias. Topical preparations containing lidocaine, benzocaine, tetracaine, and dibucaine are found in many prescription and non-prescription products, such as ointments, teething gels, suppositories, and aerosols. Lidocaine hydrochloride and benzocaine are routinely sprayed on the larynx or pharynx to control pain or laryngeal spasms during endotracheal intubation. Topical local anesthetic preparations can be hazardous if ingested or inappropriately applied to animals. Between 1995 and 1999 the ASPCA Animal Poison Control Center (APCC) consulted on more than 70 cases of local anesthetic toxicosis in a variety of animal species.

## Structure and mechanism of action

Local anesthetics vary in their chemical components, structure and activity relationships, and potency. A typical local anesthetic structure contains hydrophilic (usually a tertiary amine but may be a secondary amine) and hydrophobic (aromatic moiety) domains separated by an intermediate ester or amide linkage. A few local anesthetics do not have an amide or ester linkage. A broad range of compounds containing these minimal structural features satisfy the requirements for action as local anesthetics. These anesthetics are classified according to the type of linkage they possess, and the nature of the linkage group determines an anesthetic's pharmacologic properties. For example, local anesthetics with an ester link are readily hydrolyzed by plasma esterases. Amide-linked local anesthetics are metabolized via hepatic endoplasmic reticulum. Other factors that influence their pharmacologic properties and toxicity are hydrophobicity, molecular size, pH, and route of exposure.<sup>1</sup>

Local anesthetics bind to specific receptors within the pores of neuronal cell membrane sodium channels, blocking ion movement. This prevents neurons from reaching action potential, thereby interrupting nerve impulses and reducing pain. The action of local anesthetics is restricted to the application site and reverses when the anesthetic diffuses from the site of action within the nerve.<sup>1</sup> In addition to blocking axons in the peripheral nervous system, local anesthetics may be absorbed systemically and interfere with the function of all organs in which conduction or transmission of impulse occurs. Thus, local anesthetics affect the central nervous system (CNS), autonomic ganglia, neuromuscular junctions, and all muscles, including cardiac muscle. After absorption, local anesthetics may cause CNS stimulation and increase seizure potential.<sup>1</sup>

## Susceptibility and clinical effects

Although any animal can ingest toxic levels of local anesthetics, cats are well recognized as having hemoglobin most susceptible to the action of oxidizing agents (including aromatic amines). Thus, cats are at an increased risk for developing methemoglobinemia and Heinz body anemia with certain local anesthetics.<sup>2</sup> The oxidized form of iron ( $\text{Fe}^{3+}$ ) in hemoglobin (as seen with methemoglobinemia) increases oxygen affinity for hemoglobin and reduces oxygen release at tissues. In addition, oxidative denaturation of hemoglobin results in Heinz body formation, which can lead to erythrocyte lysis. A higher number of free sulfhydryl groups on feline globin, compared with other domestic animal species, is thought to increase the risk of Heinz body anemia in cats since oxidation of these sulfhydryl groups causes protein denaturation, leading to Heinz body formation.<sup>3</sup>

In one study, methemoglobinemia developed in seven cats after a one-second application (8.1 mg) of a benzocaine-containing topical anesthetic (Cetacaine - Cetylite Industries) to the larynx.<sup>4</sup> Two of the cats developed methemoglobin concentrations greater than 20% and cyanosis. The remaining cats developed slightly elevated methemoglobin concentrations of 2% to 6% without cyanosis. After similar application (10 mg) of a lidocaine-containing laryngeal spray (Xylocaine - AstraZeneca), there was no detectable change in methemoglobin concentrations in five cats, including one that had developed methemoglobinemia and cyanosis after receiving Cetacaine.<sup>4</sup> The study results provide sufficient evidence to recommend that Cetacaine not be used as a laryngeal anesthetic in cats.<sup>2,4</sup> Cats are sensitive to the CNS effects of lidocaine, however, so monitor them for seizures when you give lidocaine as an antiarrhythmic or local anesthetic.<sup>2</sup>

Benzocaine toxicosis cases reported to the ASPCA APCC involved either ingestion of topical preparations or application of a laryngeal spray before endotracheal intubation. Clinical signs in cats and ferrets with benzocaine toxicosis included varying degrees of vomiting, depression, cyanosis, dyspnea, and tachypnea. (ASPCA APCC Database: Unpublished data, 1995 to 1999). Additional effects seen with local anesthetic toxicosis in any species can include prolonged sedation, vasodilation (leading to hypotension), cardiac arrhythmias, respiratory depression, tremors, and seizures, and death may occur.<sup>2</sup>

Dibucaine hydrochloride, one of the most potent and toxic amide anesthetics, is about 10 times more toxic than lidocaine and 20 times more toxic than procaine hydrochloride in producing neurologic and cardiovascular effects.<sup>5</sup> It is available over the counter in 0.5% and 1% ointments and creams and may not be considered dangerous by pet owners. Dibucaine has a greater potential for fatality after ingestion than other local anesthetics. And compared with lidocaine, substantially lower doses of dibucaine may cause seizures, dysrhythmias, and death.<sup>5</sup> Clinical signs seen in cases consulted on at the ASPCA APCC in cats and dogs with lidocaine and dibucaine toxicosis included salivation, vomiting, hypothermia, depression, tremors, bradycardia, hypotension, weakness, and seizures (ASPCA APCC Database: Unpublished data, 1995 to 1999). Clinical effects include rapid progression of seizures to cardiac arrhythmias (including bradycardia, ventricular dysrhythmias, and cardiac arrest), hypotension (due to depressed cardiac contractility and vasodilation), and signs associated with methemoglobinemia.<sup>5</sup>

## Treatment

Treatment depends on an animal's presenting signs and involves stabilizing, decontaminating, and supporting the patient. Patients in respiratory and cardiac arrest need immediate intubation and cardiopulmonary resuscitation. With dibucaine toxicosis, aggressive management of hypotension, acidosis, seizures, dysrhythmias, and methemoglobinemia may be necessary. Manage seizures aggressively to prevent hypercapnia, hypoxemia, and lactic acidosis. Diazepam can be given intravenously in dogs and cats at 0.5 to 1.0 mg/kg in increments of 5-10 mg to effect.<sup>6</sup> Phenobarbital sodium (6mg/kg intravenously every 6 to 12 hours, as needed) can be used cautiously in dogs and cats with close monitoring for respiratory and cardiac depression.<sup>6</sup>

If the patient is dyspneic, administer oxygen by mask, and, by using minimal restraint, place an intravenous catheter. N-acetylcysteine may help prevent oxidative injury to hemoglobin and can be given four times a day. The loading dose in dogs and cats is 140mg/kg diluted to a 5% concentration in 5% dextrose or sterile water and given orally. Subsequent oral doses can be given at 70 mg/kg every four hours.<sup>6</sup> Intravenous fluids may be given as part of the supportive care, with close monitoring of the heart rate and rhythm, blood pressure, and respiration.

Monitor cardiovascular function carefully because hypotension and dysrhythmias are possible with local anesthetic toxicosis. Atropine sulfate administered intravenously at 0.02 to 0.04 mg/kg is indicated for sinus bradycardia in dogs and cats.<sup>6</sup> Lidocaine is contraindicated in patients with amide anesthetic toxicosis because it may augment cardiovascular and CNS toxicity. In people, bretylium tosylate is a more appropriate choice for ventricular dysrhythmias associated with amide toxicosis and may be effective in treating life-threatening ventricular tachycardia in dogs.<sup>6</sup> The bretylium dose in dogs is 2 to 6 mg/kg given intravenously.<sup>7</sup> Other ventricular antiarrhythmics that can be administered include phenytoin in dogs,<sup>7</sup> procainamide in dogs and cats, and quinidine in dogs and cats.<sup>8</sup> If hypotension is not corrected with intravenous therapy, administer dopamine hydrochloride, and closely monitor urine output, cardiac rate and rhythm, and blood pressure.<sup>6</sup>

Obtain a baseline complete blood count and serum chemistry profile, and repeat these tests during the course of the syndrome. Blood smears can be useful in evaluating the presence and degree of Heinz body formation. Methemoglobin concentrations of 15% or more will cause a brown discoloration to the blood, which is discernible on a white paper towel. Spectrophotometry quantitates percent methemoglobinemia and may be available in a local human hospital laboratory. Monitor acid-base status in symptomatic patients, especially if a patient has been having seizures. Metabolic acidosis increases the ionized fraction of dibucaine, which is responsible for toxicity, and sodium bicarbonate therapy may be indicated in dogs and cats.<sup>5,6</sup>

Vomiting can be induced in asymptomatic patients that recently ingested (less than 30 minutes) local anesthetics. But avoid inducing emesis in patients with known dibucaine ingestion because of rapid respiratory and neurologic deterioration and risk of aspiration. Activated charcoal (1 to 2 g/kg orally) and a cathartic such as 70% sorbitol (3

ml/kg orally) or magnesium sulfate (250 mg/kg or 1/4 tsp/10 lb orally) can be given in cases of recent ingestions of local anesthetics to limit further absorption; however, the patient must be stabilized before these drugs are administered, and the airway should be protected as necessary. In cases of dermal exposure, stabilize the patient, and then bathe the animal with a mild dishwashing detergent, keeping stress to a minimum.

If the patient continues to be dyspneic despite oxygen administration, consider administering polymerized bovine hemoglobin glutamer-200 (Oxyglobin-Biopure) at a one-time dose of 30 ml/kg intravenously at a rate of up to 10 ml/kg/hr. Although Oxyglobin is labeled for dogs, it has been used successfully in cats with methemoglobinemia and other disorders.<sup>9</sup> An apparently safe maximum dose rate in cats is 5 ml/kg/hr; however, it has been used at a dosage of 10 ml/kg/hr over three hours in a cat with acute blood loss.<sup>9</sup> Additionally, 50 ml over 1.5 hours (7.7 ml/kg) was given to a cat weighing 9.5 lb (4.3 kg) that had acetaminophen toxicosis.<sup>10</sup>

If methemoglobinemia is clinically evident, consider methylene blue therapy. The dose in dogs is 4 mg/kg.<sup>2</sup> Symptomatic cats can be given a single dose of 1.5 ml/kg.<sup>2</sup> Give it slowly intravenously over several minutes as a 1% solution. The dose can be repeated, but it should be used cautiously because it can potentiate the formation of Heinz bodies and anemia.<sup>11</sup> Using methylene blue in cats is controversial, and repeated administration is not recommended because of the risk of Heinz body anemia.<sup>2</sup>

As long as clinical signs are present, vitamin C therapy (20 mg/kg intramuscularly b.i.d., or 125 mg orally b.i.d.) may be of benefit because it acts as a general antioxidant and can be given to dogs and cats that have normal acid-base status.<sup>2,6</sup>

## Conclusion

Advise owners to keep medications containing local anesthetics away from children and pets and to consult a veterinarian before giving any topical or oral medication to their pets. This is especially important with dibucaine because it is a potent over-the-counter medication that can be extremely hazardous if ingested. Although the U.S. Consumer Product Safety Commission issued a ruling in 1996 requiring child-resistant packaging for products containing more than 0.5 mg dibucaine or more than 5 mg lidocaine per package,<sup>5</sup> puppies are notorious for chewing through such packaging. Avoid the topical use of any benzocaine-containing product, including Cetacaine, in cats, ferrets, or other exotic animals because of their susceptibility to methemoglobinemia.

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