Toxocologic Emergencies

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Toxicological emergencies are a common part of veterinary practice. Both dogs and cats have an amazing ability to ingest all sorts of foreign substances. Some of these substances can cause life-threatening problems while some just cause minor problems. In many situations the amount of the toxin ingested will dictate how serious the problem is. Often veterinarians work on assumptions since it is not uncommon that the actual identity of the toxin is never known. Thorough history taking and physical examinations are key in order to avoid missing a diagnosis of a toxin that requires a specific antidote. Aggressive supportive care is indicated for all those patients who ingested an unknown toxin to avoid morbidity and mortality.

Overview

History and Clinical Signs:

History from an owner is essential in the accurate diagnosis and treatment of most toxicities since clinical signs can be extremely variable. If the toxin is suspected or identified it is essential to get accurate and detailed information on the chemical or chemicals involved in order that a poison control center can be contacted for information on expected effects, treatment and prognosis. The type of toxin, the amount ingested, the time since ingestion, the clinical signs the patient is showing, and the previous medical history of the patient are all key. In the case of unknown exposure the owner should be questioned closely as to the type of chemicals, and especially medications that are available in the house that the pet might have access to. Although owners will not uncommonly try to indicate the 'neighbour has poisoned their pet' this is uncommon in the author's experience. It is much more likely that the animal ingested a natural or man-made toxin in the house or on the owner's property.

Diagnosis:

The identification of a specific toxin often requires a high index of suspicion. The clinician should work closely with poison control centers - both local human centers and any veterinary centres that are available. The National Animal Poison Control Center at the University of Illinois has a vast bank of information and is staffed 24 hours a day by veterinarians. Blood, urine and gavage samples may be required for assay to identify suspected toxins and samples of whole blood, serum, urine, and gastric contents or vomitus should be taken on admission whenever possible. If the owner has had the animal vomit at home instructions should be given to have them save the contents in a plastic bag and bring it in with the animal.

Treatment Overview

Treatment will in many cases be symptomatic unless a specific antidote is known. Fluid diuresis may be indicated. Seizure activity, ventilation and oxygenation, blood pressure and perfusion, cardiac rhythms and rates, renal function and coagulation are just some of the parameters that should be assessed and maintained as normal as possible.

Inducing Vomiting

Vomiting should be induced as soon as possible in the patient ingesting a suspected or an unknown toxin, unless vomiting is known to be specifically contraindicated (strong acids or alkalis, petroleum distillates, etc.). Apomorphine should be used intravenously for induction of vomiting. Hydrogen peroxide and salt can be given by the owner at home and are generally very effective in inducing vomiting. The dose of hydrogen peroxide is 1 to 2 teaspoons of 3% hydrogen peroxide per 10 kg body weight. This can be repeated 3 times at 5 minute intervals. Salt should be avoided whenever possible but can be given at a dose of 1/8 teaspoon per 10 kg. The sooner the toxin is out of the system the less likely toxic effects will be seen... even making the animal vomit in the car on the way to the clinic is a good idea.

Dexmedetomidine or xylazine can be used to induce vomiting in cats; however, in the author's experience neither work very well Both drugs can have serious cardiovascular side effects and the patient should be carefully assessed prior to administration of the drug and monitored for undesirable side effects.

Gastric Lavage and Activated Charcoal

Gastric lavage is widely used in small animals poisoned by ingestion of toxins. Experts are beginning to question the value of gastric lavage and it is currently not recommended in human medicine in most situations since studies have failed to confirm its value. Even when gastric lavage can be performed within minutes of ingestion, recovery of the toxin is limited. If the procedure is not completed within an hour of ingestion, recovery of many toxins is less than 15%. In small animal veterinary medicine, it is rare that gastric lavage would be completed within this period. In addition, administration of activated charcoal without lavage has shown very similar outcomes in people with many different types of toxin ingestion.

Activated charcoal should be administered via a gavage or nasogastric tube if it is indicated. Ideally a cathartic should be administered with the charcoal to hasten removal of the toxin. Many activated charcoal compounds are manufactured with cathartic (sorbitol magnesium sulfate) already present. The charcoal may need to be repeated over an extended period (sometimes 3 days) since some toxins undergo enterohepatic cycling. The decision to do this should be on a case-by-case basis. Activated charcoal often seems to stimulate vomiting which should be kept in mind when a decision is being made to administer the compound.

Skin Contamination

Skin contaminants should be rinsed thoroughly. Because these compounds also may be toxic to humans gloves should be worn. Sedation may be required with cats and aggressive animals. Make sure if sedatives are used that there is no interaction between the sedative and the toxin that might preclude its use. In many cases large volumes of warm water will suffice. In some situations washing with a mild dish soap or pet shampoo may be indicated. Make certain all soaps are rinsed from the fur and the animal should be actively dried to prevent hypothermia and avoid having the animal lick any residual chemicals from the skin during grooming.

Airway and Breathing

On presentation the patient should be checked for the presence of a patent airway and adequate ventilation. If the patient has an obstructed airway an emergency tracheotomy may be required. Patients who do not have a gag reflex should be intubated. Patients who are not ventilating adequately should have positive pressure ventilation instituted immediately. Patients with evidence of anemia, cyanosis, increased respiratory effort, or shock should have supplemental oxygen provided immediately.

If the patient has signs consistent with pulmonary edema then furosemide should be administered intravenously in addition to supplemental oxygen. If the patient will not tolerate an intravenous injection the drug should be given intramuscularly into the epaxial muscles. If the patient is extremely stressed mild sedation with an opioid or acepromazine (if the patient is hemodynamically stable) may be indicated.

If the patient has evidence of bronchospasm then supplemental oxygen should be provided and bronchodilators should be administered. Aminophylline and β–2 agonists can be given parenterally; however, in the author's experience nebulized β–2 agonists tend to be superior to parenterally administered agents. Aminophylline can cause anxiety and tachycardia whereas side effects of β–2 agonists are rare.

Circulation

Patients that are hypotensive may require crystalloids and colloids for resuscitation. Animals that are significantly anemic should receive red cells. Patients with coagulopathies should received fresh whole blood (if also anemic) or fresh frozen plasma. Patients that are hypoalbuminemic may require a combination of synthetic colloid and albumin replacement depending on the serum albumin concentration. Blood pressure and perfusion status should be returned to normal. Some toxins may cause hypotension by depressing cardiac function or by causing

excessive vasodilation. In this case positive inotropic drugs, β–blockers, antiarrhythmics, or vasopressors may be indicated depending on the toxin. Patients that are dehydrated should have their fluid deficit calculated and administered over an 8-12 hour period.

Certain toxins can cause hypertension. Systolic blood pressure greater than 200 mm Hg can lead to significant patient morbidity. The underlying cause should be identified if possible in order to treat with the appropriate drug. Nitroprusside at 0.5-10 mcg/kg/min constant rate infusion will lower blood pressure in many patients and can be titrated to effect. Acepromazine will cause hypotension through vasodilation but can be difficult to titrate. If hypertension is associated with tachycardia then a β–blocker (propranolol at 0.02-0.06 mg/kg IV over 5 minutes) should be given. Hydralazine, angiotensin-converting enzyme inhibitors and calcium channel blockers may also be helpful in controlling hypertension depending on the underlying cause. Unfortunately many of these medications are in an oral form only which may limit their usefulness in the acute stages.

Severe bradycardia (heart rates less than 50-60 beats per minute) with concurrent heart blocks, or bradycardia associated with hypotension should be treated with atropine or glycopyrrolate. Bradycardia associated with normal to high blood pressure should not be treated with anticholinergic drugs.

A urinary catheter should be placed and urine output monitored if the animal was exposed to a nephrotoxin. Alkalinizing the urine by systemic administration of sodium bicarbonate may aid in excretion of certain toxins. The urine pH will need to be monitored in these patients to ensure the goal is being achieved.

Seizure Management

Seizures should be controlled using intravenous or intranasal diazepam. If this is unsuccessful intravenous phenobarbital should be given. Both diazepam constant rate infusions and phenobarbital constant rate infusions can be given to help maintain control of seizures. The two drugs are synergistic when given together. Phenobarbital loading may be required to achieve therapeutic phenobarbital levels. If the animal has never received phenobarbital before this generally can be achieved by giving 16 mg/kg divided into 4 doses given every 20 minutes. (A dose of 3 mg/kg will raise the blood level by approximately 5 mcg/ml.) If the patient becomes excessively sedate or loses a gag reflex the clinician may prefer not to give further doses of phenobarbital until the patient is more alert. Muscle activity during recovery from pentobarbital can be easily confused with seizure activity. Levetiracetam is often used instead of phenobarbital due to the high cost of the latter drug.

Management of Stupor and Coma

Patients who do not have a gag reflex should be intubated and positive pressure ventilation should be instituted if the animal is not ventilating adequately. The patient should be placed in a 30 degree body tilt to help minimize the risk for aspiration. Pressure on the jugular veins should be avoided. Patients should be rotated every 2-4 hours to prevent atelectasis and reduce the risk for pneumonia. Pressure points should be padded to minimize the risk of pressure sores developing. The eyes should be kept lubricated with ocular ointments and the tongue may need to be kept moistened. Chlorhexidine rinses may help minimize the colonization of the mouth with potentially pathogenic bacteria.

Mannitol may be useful in helping treat cerebral edema.

A nasogastric tube may be indicated for helping with gastric decompression if regurgitation or vomiting and aspiration. The tube also can be used to provide enteral nutrition. Sneezing can raise intracranial pressure. This is not an issue for comatose patients but if sneezing is not desirable in more aware patients then placement of a nasal tube may not be appropriate.

Management of Tremors

Tremors are best controlled by use of intravenous methocarbamol, diazepam or midazolam. Constant rate infusions may be required to control the tremors. Dosing should be adjusted to ensure the patient does not become

anesthetized. If general anesthesia is necessary to control the motor movement the patient should be intubated to help protect the airway.

Management of Temperature Abnormalities

Hyperthermia may result from excessive seizure activity, muscle rigidity, malignant hyperthermia, or a hypothalamic disorder. The patient should be actively cooled if the temperature is above 104F. While the patient is being cooled appropriate measures to secure the airway, provide oxygen, fluids and control seizures or muscle activity should be taken. Cooling can be done by running the fluids through an ice bath, and placing icepacks around the head and over superficial major vessels such as the femoral and brachial arteries. Spraying the patient with water and then placing a fan on the patient will cause evaporative heat loss. Application of topical alcohol should be avoided since it can be absorbed systemically leading potentially to alcohol intoxication. Cooling should be stopped once the patient's temperature reaches 103F. If the patient's temperature is in an extreme danger zone (greater than 105F) active core cooling may be indicated. This can be done by administering cold water enemas and cold water gastric lavage. These patients frequently develop the systemic inflammatory response syndrome with all of its accompanying complications (hypotension, vasculitis with secondary albumin loss and third-spacing of fluids, coagulopathy, and multiple organ failure).

Hypothermia can be caused by certain toxins that depress the patient's level of consciousness or reset the hypothalamus. Certain medications used to treat toxicities that depress the metabolic rate (opioids, anesthetic agents, etc.) can also lead to hypothermia. Any patient that has a depressed level of consciousness should be kept warm with warm intravenous fluids, blankets, warm water circulating blankets, etc. Patients that require long term ventilation can be cooled significantly from the cold oxygen in the circuit and ideally an air warmer should be placed in the circuit. Spontaneous ventricular fibrillation can occur if the temperature drops to 28C.

Anticoagulant Rodenticide

Mechanism of Toxicity: Interferes with production of vitamin K dependent clotting factors (II, VII, IX, X) leading to active hemorrhage.

History and Clinical Signs: Signs relate to hemorrhage which can be external or internally into any body cavity, tissue space, or organ. Clinical signs generally take a minimum of 48 hours to develop and more serious signs usually indicate exposure 4-5 days prior to presentation. Hemorrhage around the larynx can cause an acute upper airway obstruction. Life-threatening hemorrhage can occur into the lungs and mediastinal tissues.

Specific Diagnostic Tests: Prothrombin time, activate partial thromboplastin time, activated clotting time, PIVKA (proteins induced by vitamin K absence or antagonism) test. Prothrombin time will prolong first and return to normal first.

Treatment: Animals who have ingested the toxin should have vomiting induced.

Animals with clinical signs should have supportive care provided (see above). Vitamin K1 should be given subcutaneously at a loading dose of 5 mg/kg followed by 5 mg/kg divided every 12 hours for 2-3 weeks for first generation coumarins and 4-6 weeks for second and third generation coumarins. Once the patient is able to take oral medications the vitamin K1 can be given orally.

If the owner is uncertain whether or not the pet actually ingested the toxin or ingested sufficient to induce hemorrhage the prothrombin time can be monitored on a daily basis for 3 days. If at 72 hours there is no evidence of a prolonged prothrombin time treatment is not necessary.

Pyrethrin

Source: Insecticides especially flea products

Mechanism of Toxicity: Neurotoxin (prolongs sodium conductance and antagonizes GABA)

History and Clinical Signs: Pets have usually been exposed to topical or premise spray products. Clinical signs include depression, muscle fasciculations, salivation, vomiting, bronchospasm and ataxia.

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Treatment: Skin decontamination should be performed if this was the route of exposure. Vomiting can be induced if the patient ingested the toxin within the previous 1-2 hours and the animal is neurologically stable and able to protect its airway against possible aspiration and the product did not contain petroleum distillates. Atropine can be used to control salivation as long as the patient is not tachycardic. Most patients recover within 24-48 hours with supportive care.

Metaldehyde

Source: Slug or snail bait

Mechanism of Toxicity: Unknown

History and Clinical Signs: Signs usually appear within 15 minutes to 3 hours of ingestion. Early signs include anxiety, salivation, panting, ataxia and possibly mydriasis and nystagmus. Later signs include muscle fasciculations, hyperthermia, and possible seizures.

Diagnostic Tests: Stomach contents, urine, plasma or tissue can be analyzed for metaldehyde.

Treatment: Emergency treatment to secure an airway, establish intravenous access and control seizures may be required. Gastric lavage should be performed followed by administration of a single dose of activated charcoal. Patients should be placed on a constant rate infusion of methocarbamol or diazepam to control the muscle tremors.

Garbage

Mechanism of Toxicity: Bacteria can release endotoxins and exotoxins. Molds can cause gastrointestinal irritation, hepatotoxicity or neurotoxicity.

History and Clinical Signs: Signs usually include vomiting and/or diarrhea. Endotoxemia can lead to the systemic inflammatory response syndrome (SIRS) and multiple organ failure. Certain toxins such as botulism can cause muscle tremors, ascending flaccid paralysis and coma.

Diagnostic Tests: Because garbage intoxication can mimic many other disease processes a full diagnostic workup is indicated.

Treatment: There is no antidote. Appropriate supportive and symptomatic care should be provided. This may need to be very aggressive care if there is evidence of endotoxemia. Supportive care may be indicated for several weeks if flaccid paralysis develops. Broad spectrum antibiotics such as penicillin, ampicillin and/or metronidazole are indicated in all cases of suspected garbage intoxication.

Chocolate

Mechanism of Toxicity: Theobromine is a phosphodiesterase inhibitor that causes an increase in cyclic AMP and a subsequent increase in catecholamines. Unsweetened baking chocolate and cocoa contain very high levels of theobromine. Dark chocolate also contains very high levels. Milk chocolate contains approximately one-tenth the amount found in unsweetened chocolate.

History and Clinical Signs: Vomiting and diarrhea may be present that are not direct causes of the theobromine but are related to the dietary indiscretion. Pancreatitis may be seen depending on the type of chocolate that was

eaten. Clinical signs include cardiac abnormalities (tachycardia, arrhythmias), central nervous system excitement (hyperactivity, tremors, seizures), panting, and urinary incontinence.

Treatment: Appropriate symptomatic and supportive care should be provided. Activated charcoal should be administered. Electrocardiographic monitoring is indicated in severe intoxications and arrhythmias should be treated appropriately.

Ethylene Glycol
Source: Antifreeze, windshield de-icing fluid, solvent in many chemical solutions

Mechanism of Toxicity: Ethylene glycol is oxidized to glycoaldehyde by alcohol dehydrogenase. Glycoaldehyde is oxidized to glycolic acid and then to glycoxylic acid. Glycoxylic acid is metabolized primarily to oxalic acid, which combines with calcium to form calcium oxalate crystals. Other end products include glycine, hippuric acid, formic acid, oxalomalic acid and benzoic acid. Ethylene glycol is an alcohol that can cause central nervous system depression and gastrointestinal irritation. It also inhibits the cytochrome P450 system which leads to increased production of oxygen radicals. The accumulation of acids can lead to a severe metabolic acidosis. The acid metabolites also interfere with oxidative phosphorylation glucose metabolism and protein synthesis and are toxic to renal epithelium. Calcium oxalate crystal deposition occurs in all organs including the brain. The minimum lethal dose is 1.5 mL/kg in cats and 6.6 mL/kg in dogs. Many solutions containing ethylene glycol also contain other toxins.

History and Clinical Signs: An environmental toxin, exposure typically occurs secondary to the animal drinking fluid that has leaked from vehicles and drinking from toilets that have been treated to prevent freezing. Early signs, which can be seen within 30 minutes of exposure and may last 12 hours may include nausea, vomiting, central nervous system depression and signs of "being drunk". Polyuria and polydipsia may be seen secondary to the osmotic diuresis. Signs consistent with renal failure typically develop within 12-24 hours in cats and within 36-72 hours in dogs.

Diagnostic Tests: Serum ethylene glycol levels can be measured or estimated using a colourimetric test. The colourimetric test is not sensitive enough for cats although if the test is positive the cat definitely ingested a toxic dose.

Treatment: Vomiting should be induced within 30 minutes; after that time it is not likely to be effective due to the raid absorption rate. Activate charcoal is not effective. Treatment includes treatment and monitoring as for any renal failure patient. A central line and a urinary catheter are advised in order to be able to monitor central venous pressure and urine output respectively. Primary treatment involves administration of an antidote, either ethanol, which acts as a competitive substrate for alcohol dehydrogenase, or 4-methylpyrazole, which is an alcohol dehydrogenase inhibitor. Ethanol has many side effects; therefore; 4-methylpyrazole is preferred. The prognosis is excellent if dogs are treated with 4-methylpyrazole within 5 hours and cats within 3 hours. Dialysis is always advised but is probably unnecessary if 4-methylpyrazole is being administered early. Dialysis is continued until the ethylene glycol test is negative which usually requires 24-32 hours of continuous dialysis.

<u>Ethanol</u>
Administer 0.6 g/kg 7% ethanol intravenously or 0.6 g/kg 20% ethanol orally as a loading dose. Then begin 100 mg/kg/hr constant rate infusion of 7% ethanol. If intravenous therapy is not an option ethanol can be administered via a nasogastric tube; however, vomiting can be a problem when given by this route. Supplement fluids with multiple B vitamins. Treatment should be continued until the ethylene glycol test is negative (minimum 36 hours).

Acetaminophen
Source: Prescription and over-the-counter drugs

Mechanism of Toxicity: Acetaminophen is metabolized to non toxic and toxic metabolites. Glucuronidation and sulfation as well as combination of toxic metabolites with glutathione are key to minimizing the toxic effects of acetaminophen. The toxic metabolites cause direct cellular death and methemoglobinemia.

History and Clinical Signs: Dogs will present with signs consistent with liver failure. Cats will present with signs consistent with methemoglobinemia (cyanosis, respiratory distress, brown mucous membranes, brown blood) as well as facial edema. Cats are extremely susceptible to the drug since they cannot efficiently metabolize it.

Treatment: Appropriate supportive care should be provided. Gastric decontamination and activated charcoal administration are warranted. N-acetylcysteine is given at 240 mg/kg loading dose followed by 140 mg/kg every 4 hours for 3 days in dogs or 70 mg/kg every 6 hours for 3 days in cats. This can be given orally or intravenously. Vitamin C at 30 mg/kg orally or subcutaneously or 20 mg/kg intravenously may help convert the methemoglobin to oxyhemoglobin. Because cimetidine interferes with the metabolism of the acetaminophen its administration may be warranted.

Strychnine
Source: Pesticide

Mechanism of Toxicity: Strychnine antagonizes glycine which is an inhibitory neurotransmitter. Most signs relate to inhibition of glycine released by Renshaw cells which are neurons that mediate the activity of antagonistic muscle groups. Inhibition of these neurons leads to uncontrolled muscle contraction. Persistent muscle activity can lead to muscle injury, hyperthermia and rhabdomyolysis.

History and Clinical Signs: Early signs included anxiety and restlessness. Tonic muscle contractions of the extensor muscle groups become evident. A risus sardonicus is evident from facial muscle contraction. Muscle contractions are worsened by external stimuli. Tetanic contractions of the respiratory muscles can lead to apnea.

Diagnostic Tests: Vomitus, stomach contents, serum, or urine can be analyzed.

Treatment: Appropriate symptomatic and supportive care should be provided. Activated charcoal is indicated. Because of the mechanism of action of the toxin gastric lavage with a protected airway is preferred if clinical signs are evident. Muscle relaxation can be achieved using methocarbamol. Diazepam may be effective. More severe muscle contractions may need to be controlled with pentobarbital. Positive pressure ventilation may be required in serious cases. The patient should be kept sedated in a darkened, quiet room to avoid exacerbation of muscle activity.

Zinc
Source: Hardware, sun-block preparations, ointments, American pennies minted after 1982

Mechanism of Toxicity: Mechanism generally unknown – thought to interfere with enzyme function. Gastric irritant.

History and Clinical Signs: Gastrointestinal signs include vomiting, diarrhea and anorexia. Mores serious toxicity causes hemolytic anemia. Acute renal failure is possible.

Diagnostic Tests: Radiographs may reveal metallic foreign material. Laboratory tests abnormalities may be consistent with hemolytic anemia or renal failure. Serum, urine and tissue can be analyzed. Special tubes may be required to handle samples appropriately.

Treatment: Appropriate symptomatic and supportive care should be provided. Activated charcoal is indicated in acute toxicities. Metallic foreign bodies should be removed. Red blood cell transfusions, treatment for

disseminated intravascular coagulation, and treatment for acute renal failure may be required. Chelation with calcium EDTA may be indicated.

Mushrooms
Mechanism of Toxicity: Varies with type of mushroom. General toxic effects include central nervous system abnormalities (hallucinations), cellular damage (organ death), and autonomic nervous signs. Gastrointestinal irritation is common.

History and Clinical Signs: Clinical signs will depend on the mechanism of the toxin.

Treatment: Appropriate symptomatic and supportive care should be provided. Gastric decontamination and administration of activated charcoal are indicated. Close monitoring of liver and renal function is indicated. Dextrose supplementation may be required to maintain euglycemia along with plasma to treat coagulopathies.

References available on request.