Why So Depressed? Nervous System Depressants

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Toxins that affect the nervous system can vary in clinical signs depending on the dose and route of exposure. The brain is susceptible to injury as it receives a high percentage (20-25%) of cardiac output, and requires a continual high level of oxygen and nutrient supply. The blood-brain barrier and blood-cerebrospinal fluid barrier help protect the brain from toxins. See table 1 for a list of some CNS depressants.

Marijuana

Over the past few years there has been an increase in the number of marijuana intoxicated pets presented to veterinary clinics. It is unknown if this is truly an increase in cases, if people are more willing to seek veterinary care due to changing attitudes about marijuana or if more potent forms of marijuana are prompting pet owners to seek medical attention.

Marijuana (Cannabis sativa) is used both recreationally and medicinally by people. It is thought to be the most commonly used illegal substance worldwide, with nearly half the population in the United States reporting at least one time use. Marijuana has been used as an anti-emetic, analgesic, anticonvulsant, muscle relaxant, appetite stimulant and to decrease intra-ocular pressure in glaucoma. Currently in the United States, there are 25 states that legally allow cannabis for medical use and five states (Alaska, California, Colorado, Oregon, Washington) and the District of Columbia, have legalized small amount of cannabis for recreational use by adults age 21 years of age and older. However, it is still a Schedule I controlled substance under the US Controlled Substances Act.

The main toxic principle of marijuana is a resin called tetrahydrocannabinol (THC), but the plant contains over 60 cannabinoids and cannabinols. The amount of these resins will vary with plant variety, sex of plant (female plant, "sensemilla" more toxic), geographic location, and growing season. THC acts via stimulation of cannabinoid receptors throughout the body. Cannabinoid receptors found in the pain pathways of the brain and spinal cord mediate its analgesic effects. The antiemetic properties are thought to be secondary to the effect of cannabinoid receptors within the central nervous system. d-9-THC also affects dopaminergic, cholinergic, noradrenergic, serotonergic, and GABA sites. There are 2 main cannabinoid receptors, CB1 and CB2. CB1 receptors, primarily found in the CNS, are associated with psychoactive effects, and peripheral CB2 receptors are associated with the immune system, responsible for the immunomodulatory effects of cannabinoids.

In the past, most pet exposures to marijuana were ingestions of plant material from baggies or joints. This has changed and now edibles (cookies, brownies, etc.) and concentrates (oils, waxes, shatters) have become more popular. Through selective breeding, THC levels have become higher than ever. The University of Mississippi Potency Monitoring Project has reported that THC levels have more than doubled over the last 25 years. THC levels in plant material ranges from 1-8%, extracts 28%, and hash oil up to 50%. Another change has been the increase in marijuana butter based edibles. THC butter is made by heating marijuana in butter to extract the lipophilic THC. This butter is then used to make the baked goods. While both dogs and cats willing ingest plant material, dogs are the most likely to consume edibles. Many of the edibles also incorporate chocolate and this can increase the toxicity.

Another issue with THC containing products is quality control. In one study, 75 products were evaluated to determine the amount of cannabidiol and THC found in the various products. The results indicated that 17% of products were accurately labeled, 23% were under labeled and 60% were over labeled with respect to THC content.

The most common clinical signs after ingesting marijuana are ataxia, lethargy, and urinary incontinence. However, about 25% of patients may present stimulated instead. Hyperesthesia and disorientation are also frequently seen along with bradycardia, hypothermia, mydriasis, and tremors. Animals that get into concentrates or THC butter products may become comatose and hypotensive. Clinical signs can be seen as soon as 30 minutes after oral ingestion and may last up to 72 hours.

Urine drug screening tests have not been validated for use in dogs. Most over-the-counter urine drug tests will give a false negative result for marijuana (THC) in dog urine. This is thought to be due to different metabolites produced by dogs when compared to humans (8-OH-Δ^9-THC produced by dogs vs. 11-OH-Δ^9-THC in humans). These different metabolites may also explain the urinary incontinence that is seen in dogs and not in other species.

As marijuana is an anti-emetic, inducing emesis may not be successful but can be tried with recent (< 30 minutes) oral exposures if the animal is asymptomatic. Activated charcoal is generally not needed. Intravenous fluid administration should be started and adjusted if dehydration or hypotension develops. Diazepam or low dose acepromazine (if normotensive) can be used for agitated patients. Monitor blood glucose levels in young animals. Many cases with plant material ingestion can be managed at home with confinement and monitoring the ability to ambulate.

For more symptomatic animals, monitor respiratory function, heart rate, blood pressure and body temperature. Keep animal warm, quiet, minimize sensory stimuli, and rotate body position q 4 hours if the animal is recumbent. Intralipids (20% solution) may be helpful for severely affected (comatose) animals because THC is lipid soluble, but results have been variable. The dosing regime is a 1.5 ml/kg initial bolus (over 20-30 minutes) then a CRI of 0.25 ml/kg/min for 30-60 minutes. Repeat CRI in 4 hours provided there is no lipemia. No specific CBC or chemistry profile abnormalities are expected. There is no role for dialysis, hemoperfusion, urinary alkalinization or multiple dose charcoal in the management of marijuana toxicosis. THC is highly protein bound (97% to 99%) and has a large volume of distribution (10 L/kg, with high lipophilicity), and thus dialysis or hemoperfusion has no theoretical benefit.

Toxicity is dose-related; however, there is a wide range of variability among individuals. Patients with hepatic impairment may be more sensitive. A lethal dose has not been established in dogs or cats, but it only takes a small amount to cause clinical signs. Fortunately death is rare. There are published reports of two dog deaths after ingesting edibles and a 12-week-old ferret after ingesting plant material. If appropriate treatment is implemented, the prognosis is good and no permanent effects should be anticipated.

Baclofen

Baclofen is a centrally acting skeletal muscle relaxant that mimics γ-aminobutyric acid (GABA) within the spinal cord and causes a flaccid paralysis of skeletal muscles. At oral therapeutic levels, baclofen has virtually no CNS effects due to its poor ability to cross the blood brain barrier, but in overdose situations, CNS effects are common. The most common clinical signs of toxicosis are vomiting, ataxia and vocalization/disorientation, but the most life

threatening signs are dyspnea, respiratory arrest and seizures. Dyspnea and respiratory arrest are secondary to paralysis of the diaphragm and intercostal muscles.

The onset of clinical signs varies in dogs with signs occurring anywhere from 15 minutes to 7 hours post exposure (average of 1.9 hrs.). Duration of clinical signs varies from several hours to several days. Signs can continue long after serum baclofen levels have returned to normal due to the slow clearance from the CNS. Dog doses as low as 1.3 mg/kg can cause vomiting, depression and vocalizing. There are no established lethal doses in animals, but per the APCC data base, deaths in dogs have occurred at doses as low as 8 mg/kg.

Due to the rapid onset of clinical signs, emesis should be considered in only the asymptomatic, recently exposed patient. Gastric lavage may be considered with large ingestions, but care must be taken to ensure that anesthesia does not compound CNS depression. Short acting induction agents such as propofol, followed by inhalent anesthesia with a protected airway are preferred. All asymptomatic cases should receive activated charcoal with a cathartic. Avoid magnesium-based cathartics (Epsom salts), as they may worsen CNS depression. Exposed animals should be monitored for 12 hours for development of clinical signs.

Ventilatory support is a prime concern and endotracheal intubation and positive pressure mechanical ventilatory support may be needed for an extended time in severe cases. Diazepam is the drug of choice for centrally acting skeletal muscle relaxant induced seizures. Propofol or isoflurane may be considered in cases that are refractory to diazepam. Long acting barbiturates or other agents that produce profound or prolonged CNS depression should be used with care. Cyproheptadine (1.1 mg/kg PO or rectally) has been used successfully to reduce the vocalization/disorientation seen in some animals. Fluid diuresis is used to enhance elimination and maintain blood pressure. Intralipids have been used successfully in early intoxications. The use of CNS respiratory stimulants is of questionable value and experimental studies have failed to consistently produce positive outcomes when flumazenil was used and have potential to cause serious adverse effects (seizures). Prognosis is variable, and can depend on the availability of ventilatory support for depressed patients. Prognosis is more guarded if seizures develop.

Opioids and Opiates

There are many opioids and opiates used in human and veterinary medicine. Opioids and opiates are synthetic or natural compounds derived from the opium poppy, *Papaver somniferum*, and are generally classified (agonist or partial agonist) by their ability to exert effects at the different opioid receptors (mu, kappa, delta, sigma). Partial agonists are agonists at one (or more receptors) and antagonists at others. Opioids act centrally to elevate the pain threshold and to alter the psychological response to pain. Most of the clinically used opioids exert effect at the mu receptor (mu_1 subtype mediates analgesic effects, mu_2 mediates respiratory depression).

Opioids are well absorbed from the GI tract, but bioavailability is variable as some opioids have a large first pass effect (i.e. fentanyl). These opioids are administered in other manners (CRI, buccal, transdermal) to reach therapeutic blood levels. Metabolism varies, but opioids generally undergo hepatic metabolism (conjugation, hydrolysis, oxidation, glucuronidation, or dealkylation). This glucuronidation may account for the sensitivity of cats (who are deficient in glucuronyl-S-transferase) to opioids.

In dogs, CNS signs include depression, ataxia, and seizures. Respiratory depression, vomiting, bradycardia, and hypotension may be seen. Cats may show excitatory behavior and urinary retention. Detection of opioids can be made from urine or serum samples.

Treatment in an asymptomatic animal may include emesis if the ingestion is recent. Activated charcoal with cathartic should be administered and the patient monitored for up to 12 hours. If the animal becomes symptomatic, naloxone (0.1-0.2 mg/kg IV, IN, IM or SQ) can be administered. As the duration of action of naloxone is much shorter than that of the opioids, repeat dosages may be necessary. Partial agonists/antagonists (i.e. butorphanol) may be used to partially reverse pure agonists if no naloxone is available. Monitor temperature, cardiac function and blood gases. Treatment times will vary with the half-life of the opioid. If respiratory and cardiovascular function can be maintained then prognosis is good. For those cases that are seizuring, prognosis is guarded.

DRUG	ACTIVITY	Mu	Delta	Kappa$_1$	Kappa$_2$
Morphine	Agonist	+++		+	+
Fentanyl	Agonist	+++			
Butorphanol	Agonist/antagonist	P	NA	+++	NA
Buprenorphine	Agonist/antagonist	P	NA	--	NA
Naloxone	Antagonist	---	-	--	--

(P = partial)

***Fentanyl*:** Fentanyl suckers, lozenges and transdermal patches are becoming more frequently used in both human and veterinary medicine. The lozenges or suckers contain fentanyl citrate in a sucrose and liquid glucose base and are attractive to animals. The patches have poor absorption from the GI tract, but can be absorbed transmucosally while the animals are chewing on them. Signs are similar to other opioids with depression, bradycardia, hypotension, weakness, and pallor predominating. Treatment is as for other opioids.

Alcohols

There are three main alcohols of concern: ethanol found in beverages, some liquid medications, and bread dough; methanol found in windshield cleaner ”antifreeze”; and isopropanol found in rubbing alcohol and some alcohol-based flea sprays. All alcohols are rapidly absorbed orally; dermal absorption can also occur. Inhalation, particularly of concentrated fumes in a confined area, can also cause systemic signs. Signs develop rapidly, often within 30-60 minutes, and include vomiting, ataxia, tremors, hypothermia, hypoglycemia, acidosis, aspiration pneumonia, respiratory depression, and coma. Methanol in humans and other primates can cause blindness, but this is not an issue in dogs and cats.

Due to rapid onset of signs, decontamination should be performed only within the first 30 minutes following ingestion. Other treatment is symptomatic and supportive and includes fluid diuresis, thermoregulation, and correction of acidosis and hypoglycemia.

Avermectins

Avermectins include ivermectin, milbemycin, selamectin, doramectin, abamectin and moxidectin. In nematodes and arthropods, avermectins bind to glutamate-gated chloride channels causing hyperpolarization by enhancing the movement of chloride ions into the cell. This results in paralysis. In mammals, avermectins cause CNS effects by potentiating the release and binding of GABA in the central nervous system. Doses of ivermectin and moxidectin in heartworm medications are safe for even MDR1 (ABCB1) deficient dogs (Collie-type breeds, Australian Shepherds, etc.). Problems arise when owners are giving large amounts to treat

dermatologic disorders or give the equine product to their pets. In general, young animals are considered more sensitive to the effect of avermectins due to a less developed blood-brain barrier. Ivermectin is well absorbed orally and the half-life in the non-sensitive dog is as long as 2-3 days. Enterohepatic recirculation is suspected based on the long half-life and extent of fecal excretion (98%) of ivermectin. With the 'non-sensitive' breeds of dogs signs may be seen at 2000 mcg/kg, but only 150 mcg/kg is needed in the 'sensitive' breeds to cause signs. Cats have demonstrated clinical signs at the "therapeutic dose" of 200 mcg/kg. Moxidectin is a semi-synthetic avermectin that is much more lipid soluble than ivermectin. Therapeutic levels of moxidectin have been measured 30 minutes post oral exposure. Moxidectin has a wide margin of safety in dogs when given orally**.** Doses of up to 300 times the therapeutic dose (300 mcg/kg) resulted in little to no side effects. Most problems are encountered when dogs ingest horse dewormer.

The most common clinical signs of avermectin toxicosis include: depression, weakness, recumbency, ataxia, and coma. Other reported signs include tremors, seizures, transient blindness, bradycardia, and hyperthermia. If the exposure has just occurred and the animal is asymptomatic induce vomiting (if an oral overdose) or consider surgical debridement if given SQ and can localize injection site in massive overdoses. If the animal is symptomatic, treatment is mostly supportive care and repeated dosages of activated charcoal. Activated charcoal/cathartic should be given q 8-12 hours (sorbitol 70% -cathartic of choice) until normal. Intralipids can be given; however, efficacy is greater with moxidectin due to its higher lipid solubility. Treatment can take days to several weeks. Supportive care is very important (fluids, parenteral nutrition, frequent turning, etc.). Physostigmine can be given, but it is not an antidote. Physostigmine has a very short beneficial effect (arousal for 30-90 minutes) and should only be used in severely non-responsive dogs (not recommended for cats). The recommended dose is 0.05 mg/kg IM or IV (very slow, over 5 minutes). Prognosis depends on the speed of onset of clinical signs, the faster the onset, the worse the prognosis.

Spinosad

Spinosad is a tetracyclic macrolide anti-parasitic. It can cause vomiting and ataxia; however, if spinosad is given in conjuction with high dose ivermectin, avermectin toxicosis can develop.

Essential oils

Essential oils have been used for flea control. D-limonene is a derivative of citrus pulp. This essential oil has minimal to moderate efficacy to control fleas. If diluted properly, this product has a high margin of safety. Application of the undiluted product can cause skin and oral irritation, lethargy, vomiting, salivation, ataxia and muscle tremors. Essential oils can penetrate the skin and cause peripheral vasodilation leading to hypotension and hypothermia. Melaleuca oil is an essential oil from the Australian tea-tree, *Melaleuca alternifolia*. It does have antibacterial and antifungal properties but the efficacy of this agent to repel or kill fleas has not been established. Inappropriate application of products not intended for topical use may result in ataxia, weakness, tremors and depression. Pennyroyal oil is derived from the leaves and flowers of the pennyroyal, squaw mint, or mosquito plants. Pennyroyal oil contains a volatile compound called pulegone, which is responsible for the toxic effects of the plants. The effectiveness of pennyroyal oil to kill fleas is unknown; however, toxicity has been reported. Exposure to

pennyroyal oil may induce depression, vomiting, hepatic necrosis, diarrhea, epistaxis, seizures, and death.

Toxicity is dose-related and the possibility of severe signs is more likely if the pure oil is applied to the pet. Cats appear to be more sensitive than dogs to any of the essential oils. Treatment recommendations include bathing with liquid dishwashing detergent, activated charcoal with cathartic, pain control if needed, body temperature regulation and fluids. Most essential oils have long half-lives (days) due to enterohepatic recirculation.

References available upon request.

Table 1. CNS depressants in dogs and cats.

Pharmaceuticals	Antihistamines Baclofen Barbiturates Benzodiazepines Bromide dl-methionine Opioids Progesterone
Household/Industrial	Alcohols (methanol, ethanol, isopropyl, ethylene glycol, propylene glycol) Essential oils Turpentine
Pesticides	Amitraz Avermectins (ivermectin, moxidectin, selamectin, milbemycin) Bromethalin Imidacloprid Piperazine
Metals	Lead
Plants	Marijuana
Other	Coral snakes Any liver toxin Mohave toxin pit vipers Isoxazole mushrooms Thiaminase (raw fish)