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Neurological Emergencies

Mini Series

Session Three - Systemic causes of Neurologic Crisis - toxicity and metabolic diseases

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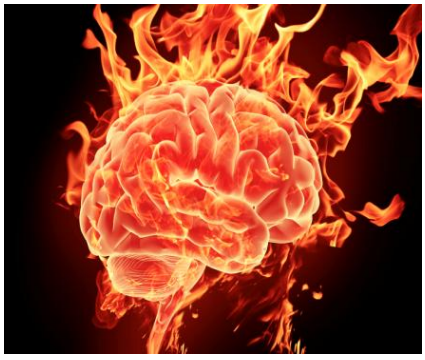

Neurotoxicity is commonly encountered in emergency veterinary practice. Toxins that cause neurological signs may be exogenous or endogenous in origin. Exogenous neurotoxins include plant or environmental toxins, envenomations, pesticides, herbicides, medications or food. Most toxins affect the neurological system directly; some may have indirect effects due to the metabolic effects of the toxin (e.g. hepatic encephalopathy due to a toxin that causes hepatic failure

The main principles of treating neurotoxicity include the following and are often performed simultaneously:

1) Systemic stabilisation
2) Symptomatic treatment
3) Decontamination and prevention of absorption of further toxins
4) Provide antidotes if available

1) Systemic stabilisation

The patient's airway should be protected using a cuffed endotracheal tube if the patient is obtunded and/or at risk of aspiration of gastric contents. Suction of the oropharynx with a Yankauer suction tip may be necessary in patients who are unable to swallow (these patients may be more easily anaesthetized and intubated in lieu of frequent oropharyngeal suctioning). Patients should be intubated and ventilated if respiratory paralysis or other causes of hypoventilation are present and oxygen should be provided if the patient is cyanotic or hypoxemic.

Maintenance of adequate blood pressure is essential for hepatic and renal perfusion, which are important for the clearance of many toxins. Systemic blood pressure should be measured and normalised, and cardiac arrhythmias should be evaluated and treated. Blood pressure may initially be measured using indirect methods (e.g. Doppler probe or oscillometric machine); normal mean arterial pressure should be near 75 mm Hg, and normal Doppler blood pressure should be above 80mm Hg. Cardiac rhythm may be assessed using an ECG, or by simultaneous palpation and auscultation for pulse deficits.

2) Symptomatic treatment

Diazepam or midazolam are first line therapy for seizures of unknown cause including toxicities. Occasionally, benzodiazepine drugs can result in disinhibition and worsening of hyperaesthesia in susceptible patients. If benzodiazepines are ineffective at stopping seizure activity, phenobarbital (phenobarbitone) may be used. If these drugs are ineffective, anaesthesia should be induced with propofol or alfaxalone. In these cases, it is imperative to maintain a protected airway with a cuffed endotracheal tube. Patients which require prolonged anaesthesia can be maintained with volatile anaesthetics (isoflurane, sevoflurane), intravenous infusions of propofol or alfaxalone, or intermittent injections or CRI's of pentobarbitone, where this is still available as a sterile solution. Long-term alfaxalone administration may result in accumulation in cats and requires gradual dose reduction in this situation. Patients with severe muscle tremors but not seizures are often best managed with methocarbamol, although benzodiazepines may also be used to provide some muscle relaxation.

- Control of body temperature

Patients with hyperthermia (rectal temperature ≥ 104 °F or 40 °C) should be aggressively cooled until the rectal temperature is 103.5 °F or 39.7 °C. Convective cooling is the most effective way to cool a patient and involves wetting the fur and placing the animal near a fan.

Application of alcohol to the paw pads is usually not adequate for cooling of hyperthermic patients, and direct application of ice packs may cause cutaneous vasoconstriction and paradoxically slow cooling. The application of wet towels to the animal will also slow cooling by impairing evaporative losses. Patients who have been hyperthermic for prolonged periods of time may develop and require treatment for heat stroke, in addition to their primary neurologic problem.

Patients presenting with hypothermia should be warmed gradually, with frequent reassessment of temperature, ECG, and blood pressure, in addition to metabolic state (e.g. blood glucose concentration). Forced warm air is the most effective way to warm a hypothermic patient and many commercial products are available that may be used for this purpose. Circulating warm water blankets may also be used, but are less effective than forced warm air.

- Maintenance of hydration and normovolaemia

Following fluid resuscitation, hydration may be maintained with any isotonic crystalloid fluid (e.g. Normosol R, lactated Ringer's solution or plasmalyte 148). In addition to maintenance needs, the effect of additional administered drugs (e.g. diuresis by mannitol or furosemide) must be taken into account. Animals with diarrhoea, vomiting, or those that are panting excessively may have iso or hypotonic fluid losses that must be accounted for.

3) Decontamination and prevention of absorption of further toxin

The methods used to prevent absorption of toxins as well as those used for decontamination will depend on the route of entry of the toxin and the metabolic profile of the toxin. Many methods accomplish both decreased absorption as well as decontamination by eliminating the toxin.

- Cutaneous toxins- Most toxins that are absorbed by a cutaneous route are lipid soluble. It is important to ensure that the patient is physiologically stable prior to bathing. Dishwashing detergent (liquid sink form, such as Dawn®) may be more effective than shampoo at removing fats and lipids. Multiple baths may be necessary to fully decontaminate the animal. Dishwasher soap preparations should not be used, and medicated shampoos should be avoided for bathing. Animal carers should wear gloves for their own safety while washing off cutaneous toxins.
- Inhaled toxins - Patients should be removed from toxic atmosphere to a well ventilated area and oxygen should be provided if indicated. Animals that have inhaled caustic substances may require mechanical ventilation and aggressive supportive care.
  - Gastrointestinally absorbed toxins- decontamination methods consist of emesis, gastric lavage and colonic lavage. Activated charcoal and/or cathartics can be used to decrease absorption of toxins.

Emesis is most successful within 2 hours of toxin ingestion and rarely successful if greater than 6 hours after ingestion. Vomiting should continue until the patient is 'dry retching' to optimise gastric content evacuation. For rapidly absorbed or small volume ingestions, and for exposures that occurred beyond the 4-6 hour window, administration of activated charcoal may be a more effective method of decontamination. Emesis is generally contraindicated in cases of ingestion of caustics (risk of worsening oesophageal injury), hydrocarbons or other volatile substances (high risk of pulmonary aspiration). It is also contraindicated in animals with obtundation, pharyngeal paresis/paralysis, dysphagia, or seizures due to an inability to protect the airway during emesis.

Gastric lavage is used when the patient's condition contraindicates emesis (usually due to profound CNS depression) but a significant volume of toxin is likely to still be present in the stomach. Generally it should be performed within 2 hours of toxin ingestion however with large volume toxin ingestions, or those that slow GI motility, it may be productive up to 6 hours post ingestion. Gastric lavage is contraindicated in cases of: ingestion of caustics and hydrocarbons, small volume toxin which could be decontaminated with activated charcoal, moderate volume of toxin ingested more than 2 hours previously and is probably no longer present in the stomach (activated charcoal could be administered instead).

Activated charcoal is indicated for adsorption of most toxins, especially when toxin may still remain in the gastrointestinal tract, or if toxin undergoes enterohepatic recirculation (i.e.,excretion of toxins into bile and reabsorption via the intestines). It is contraindicated if toxin is likely to no longer be present in

the gastrointestinal tract. It is also contraindicated if the patient is judged to have a high risk of charcoal aspiration and the airway cannot be controlled or the patient cannot be closely monitored post administration. Alcohols, petroleum products, strong acids or alkalis, dissociable salts, and metals such as iron or lithium are not adsorbed by activated charcoal. Recommended dosage ranges from 1 to 5 g/kg PO. This initial dose may be a charcoal suspension with or without sorbitol (a cathartic) and may be combined with a small amount of food, but additives may decrease effectiveness. In toxins with slow gastrointestinal release and absorption, and in toxins which undergo enterohepatic recirculation, repeated dosing should be performed at a dose of 1 -5 g/kg PO every 6-8 hours for 24 hours after exposure. With repeated dosing ensure the patient is well hydrated to avoid constipation. The charcoal preparation containing sorbitol should *not* be used for repeated dosing. Activated charcoal can be administered by stomach tube after gastric lavage if indicated, or syringe fed if the animal can safely swallow. Occasionally dogs will willingly drink the charcoal liquid. The efficacy of activated charcoal is altered by addition of mineral oils or dairy products, but the effect of small amounts of dog food or other additives is unknown. Activated charcoal is available as suspensions (available with or without sorbitol as an additive), tablets and, powdered activated form which must be made into a suspension for administration.

Lipid infusions - The infused lipid is postulated to act as a sink for lipophilic drugs, preventing further tissue absorption as well as decreasing tissue levels. The infusions are well described in the human literature for therapy of bupivacaine overdose, and may have use for other lipophilic toxicants seen in veterinary medicine. In the single veterinary case report, 20% soybean oil in water was administered as a bolus of 2 ml/kg IV, followed by a CRI of 4 ml/kg/h for 4 hours. The dose may be repeated in 6-8 hours if clinical signs are still present and the serum is not lipaemic. The dog in the case report received a second dose of 0.5 mL/kg/min for 30 minutes 15 hours after the initial infusion. Even though propofol is formulated in a lipid emulsion, it is unlikely to provide a significant lipid sink without significant systemic effects.

Specific Neurotoxins

Neurotoxins can be broadly categorized into neuro-excitatory and neuro-inhibitory according to the predominant neurological signs present.

Neuro-excitatory toxins affect the central nervous system causing hyper-excitability and seizures and/or affect the peripheral nervous system causing muscle tremors and fasciculations. Ataxia may also occur. Possible systemic complications associated with neuro-excitatory toxins can also include heat stroke (and subsequent complications such as disseminated intravascular coagulopathy [DIC]), rhabdomyolysis, aspiration pneumonia, and secondary neurologic injury.

Neuro-inhibitory toxins either affect the CNS causing obtundation, stupor and coma and/or affect the peripheral nervous system causing weakness or flaccid paralysis which, at its most severe, includes respiratory paralysis.

NEURO-EXCITATORY TOXINS

BROMETHALIN

Overview:

- Bromethalin is a rodenticide that was developed to use against warfarin-resistant rats and mice.

Mechanism of action:

- Bromethalin leads to uncoupling of oxidative phosphorylation and a subsequent decrease in ATP production in the cell.

        - Inhibition of ATP production leads to dysfunction of the Na+/K+ ATP-ase pump within the CNS and an increase in intracellular sodium concentrations.
        - Water then moves into the cells and results in cerebral oedema, increased volume of CSF and vacuolization of myelin. This may result in increased intracranial pressure, axonal damage and ultimately inhibition of neural transmission.
    - LD_{50} in dogs is 4.7 mg/kg and 1.5 mg/kg in cats.
    - Standard packages contain between 15 and 45 grams of 0.01% bromethalin.

Clinical signs:

- Higher doses produce acute signs of hyperexcitability, hyperesthesia, muscle tremors, focal or generalized seizures and hyperthermia within 2-24 hours of ingestion.
- Low to moderate doses produce the more common clinical presentation of hindlimb ataxia, extensor rigidity, decreased conscious proprioception, and paresis that can progress to paralysis.
    - CNS depression is also usually present, with more severely affected animals becoming comatose.
    - These signs may not manifest until1-3 days after exposure.
- In the later/terminal stages, animals may develop seizures and a decerebrate posture.
- Cats may experience a slower onset and longer duration of clinical signs than dogs.

Diagnosis:

- Antemortem diagnostics are not available for bromethalin.
- Bromethalin or its metabolite can be detected in the liver, kidney, and brain. Samples should be submitted frozen and protected from light.

Treatment:

- No antidote is available.
- Decontamination: Induction of emesis or gastric lavage should be performed to remove any bromethalin within the stomach.
- Prevention of absorption: Repeated doses of activated charcoal (1-5 g/kg every 6-8 hours) should be administered for at least 48 hours after ingestion to decrease absorption and reduce enterohepatic recirculation of the bromethalin and its metabolites. Use of a cathartic (sorbitol) is recommended with the initial dose of activated charcoal.
- Symptomatic treatment: Methocarbamol (44mg/kg IV) can be used for controlling excessive muscle tremors, diazepam (0.5 mg/kg IV) for seizures, and mannitol (0.5 – 1 g/kg) or 7% hypertonic saline (1-3 mL/kg) to help reduce cerebral oedema.
- Supportive care should focus on maintaining normal cardiovascular parameters (heart rate and blood pressure) in an effort to maximize cerebral perfusion pressure. Care should be taken to avoid hyperthermia and hypercapnia. Bladder management, nutrition supplementation, and general nursing care should be instituted in paretic patients.
- Use of corticosteroids has previously been suggested for bromethalin toxicosis, however there is no evidence to support this recommendation and thus their use is not indicated.

Prognosis

- Prognosis is guarded to grave due to the severity of clinical signs seen at even low doses of exposure, as well as lack of an antidote.
- Animals with mild clinical signs can recover and full resolution of clinical signs may take several weeks, however some will have permanent neurologic dysfunction.

IVERMECTIN and other macrolide antiparasitics

Overview:

- Drug class is also known as avermectins or macrocyclic lactones and includes ivermectin, moxidectin, selamectin, milbemycin, doramectin, eprinomectin and abamectin
- Toxicity may occur secondary to ingestion of large animal deworming products or contaminated faeces
- Overdose may be iatrogenic if owners inappropriately administer topical products per os; or inappropriate doses of anti-parasitic medications
- A high percentage of collies and related herding breeds of dog have an increased genetic susceptibility for toxicity due to ineffective blood-brain barrier efflux pumps.

Mechanism of Action:

- Macrolide antiparasitic drugs cause toxicity in mammals by acting as agonists at the γ-aminobutyric acid ($GABA_A$)-gated chloride channels in the CNS. Initially this may result in neuroexcitation but at higher doses can result in flaccid paralysis and coma.
- Collies, border collies, shelties, Australian Shepherds, Shetland sheepdogs and herding breeds of dogs have a high incidence of a mutation in p-glycoprotein (MDR1), which serves as an efflux pump for lipophilic compounds in the CNS. This results in increased accumulation of the drug within the CNS and clinical signs of neurotoxicity at doses safe for dogs without this mutation.
- Occasionally dogs from breeds not previously reported to have increased susceptibility to avermectins may develop signs of toxicity at low doses.
- Toxicity in dogs is unlikely to occur at prophylactic heartworm doses of ivermectin (6 mcg/kg) even in susceptible breeds. Ivermectin toxicity in susceptible dogs may occur at doses as low as 0.1 mg/kg, whereas non-susceptible breeds may not develop toxicity until doses of 2.5 mg/kg are exceeded.
- The LD_{50} for beagles has been reported to be 80 mg/kg.
- Cats may be more sensitive to ivermectin, and 0.3 to 1.3 mg/kg administered SQ may be enough to cause l signs of toxicity.
- Many of these drugs have long half-lives for elimination; in dogs this ranges from 2 days for ivermectin to 19 days for moxidectin.
- Enterohepatic recirculation does occur.

Diagnosis:

- History of exposure or iatrogenic administration of macrolide drugs.
- Testing for MDR1 genotype to assess for defective p-glycoprotein in dogs who appear to have increased susceptibility. These animals will likely have increased sensitivity to other drugs such as opioids.
- Some laboratories will assay blood levels of macrolides

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Clinical Signs:

- Signs of toxicity in dogs and cats include ataxia, lethargy, tremors, mydriasis, blindness, hypersalivation, disorientation and seizures. This may progress to weakness, stupor, coma and respiratory failure.

Treatment:

- In cases of recent ingestion, emesis may be induced, as long as the animal is alert. If the animal is stuporous or comatose and a large amount was ingested, gastric lavage may be considered.
- Repeated doses of activated charcoal 1-5g/kg every 6-8 hours for 6 treatments.
- Use of intravenous lipid infusion may limit the duration or severity of clinical signs.
- Seizure control
    - Achieved primarily using barbiturate drugs such as phenobarbitone.
    - Historically, benzodiazepines were thought to exacerbate clinical signs of avermectin toxicoses, due to proximity of binding sites on the GABA receptor, and thus were not recommended as first line seizure control. It has been recently postulated that this may not be the case.
    - If sedation or prolonged anaesthesia is required, a propofol CRI is a better option than repeated benzodiazepine administration.

Prognosis:

- Prognosis is guarded if ivermectin dose received is > 5mg/kg
- Recovery may be prolonged, especially in animals exposed to a longer lasting drug such as moxidectin, taking 2-3 weeks for full recovery.

MYCOTOXINS (TREMORGENIC)

Overview:

- The most common tremorgenic mycotoxins are Penitrem A (produced by Penicillium crustosum) and Roquefortine (producted by Penicillium roquefortine and other penicillium species).
- Other less common tremorgenic mycotoxins have been reported. Mouldy foods (nuts, garbage, soft cheeses) and compost may all be sources.
- Penitrem A is most likely to be produced in food materials that have high moisture content.

Mechanism of action:

- The actual mechanism of toxicity is unknown, but is thought to be related to the inhibitory actions of glycine in the CNS. It is possible that the toxin inhibits glycine release or antagonises the actions of glycine in inhibitory neurons. There is also a possibility that some mycotoxins result in increased presynaptic neurotransmitter release.
- Toxic dose: In one small study of intraperitoneal toxicity of Penitrem A in dogs, doses from 0.125mg/kg resulted in tremors and doses of 0.5mg/kg to 5mg/kg also resulted in intermittent periods of seizure activity and finally death in the majority of untreated dogs. Seizure length and severity appeared to worsen with higher doses.
- Both penitrem A and roquefortine are rapidly absorbed after oral ingestion. They are excreted via bile, and enterohepatic recirculation may occur.

Clinical signs:

- Onset of signs can occur 30 minutes to several hours post ingestion.
- Hyperaesthesia, anxiety, restlessness, panting, vomiting, salivation, mild to severe muscle tremors and fasciculations, seizures, status epilepticus.
- Potential for hyperthermia, heat stroke and rhabdomyolysis secondary to tremors.

Diagnosis:

- History or suspicion of ingestion of mouldy food
- Identification of Penitrem A or Roquefortine in vomitus or food material via mass spectrometry, thin layer chromatography or quantitative analysis via high pressure liquid chromatography.
- If toxin identification is unavailable then culture of food or vomitus and growth of *Penicillium* or other mycotoxin producing fungus is compatible.

Treatment:

- Gastrointestinal decontamination: emesis or gastric lavage if recent or large volume ingestion. Activated charcoal should be administered q 6 hours for 24 hours because of enterohepatic recirculation of toxins.
- Control tremors: Benzodiazepines +/- methocarbamol. May also use phenobarbitone for tremor/seizure control. In severe cases, general anaesthesia may be required.
- Supportive care as indicated.

Prognosis:

- Prognosis is generally good with appropriate supportive care and effective gastrointestinal decontamination. However prognosis is guarded if gastrointestinal decontamination is incomplete in the face of a large dose of ingested mycotoxin.
- Recovery can be very rapid but commonly occurs over 24 to 48 hours and occasionally is prolonged up to 4-5 days.

ORGANOPHOSPHATES and CARBAMATES

Overview:

- These toxins are commonly used in agriculture and for domestic garden and household pest use. Additionally these are also used for external parasite control.
- Pets are generally exposed by ingestion or dermal exposure.

Mechanism of action:

- Organophosphates and carbamates inhibit the action of the acetylcholinesterase enzyme (AchE) allowing acetylcholine to accumulate at cholinergic synapses.
- Continued stimulation at parasympathetic synapses results in excessive stimulation of the distal neuron, gland or muscle, causing (i) familiar cholinergic signs of muscarinic toxicity which include salivation, lacrimation, urination, and defecation (SLUD), in addition to bronchospasm, (ii) CNS toxicity (depression and decreased levels of consciousness), and (iii) nicotinic toxicity (weakness and muscle tremors).
- Organophosphates bind tightly to AchE and can become permanently bound which is known as ‘aging’ of the AchE.
- There are 3 syndromes associated with organophosphate toxicity:
    - Acute toxicity
    - Intermediate syndrome for which the underlying pathology has not been determined
    - Organophosphate induced delayed neuropathy (OPIDN) which is a toxin induced degeneration of the long motor nerves.
- Carbamates do not become permanently bound and bind to AchE for a significantly shorter period, generally less than 40 minutes.

Clinical signs:

- Acute toxicity presents with a combination of muscarinic, nicotinic and central signs.
    - Muscarinic clinical signs include hypersalivation, lacrimation, urination, defecation, diarrhoea, vomiting, miosis, bradycardia, bronchospasm and bronchorrhea. Respiratory compromise may result in cyanosis. Tachycardia and mydriasis may be present secondary to catecholamine release.
    - Nicotinic clinical signs include muscle fasciculations, muscle twitches and tremors. Weakness and paralysis can be a delayed neuromuscular sign.
    - Central nervous system signs include anxiety, ataxia, seizures, obtundation and coma
- Intermediate syndrome- develops 7 to 96 hours after an acute OP toxicity.
    - Clinical signs of severe neuromuscular weakness are present particularly affecting the cranial half of the body with cervical ventroflexion, forelimb weakness and hypoventilation reported.
- Chronic toxicity or exposure can cause organophosphate induced delayed neuropathy (OPIDN)
    - This generally occurs 1- 4 weeks after exposure to the OP. Anorexia, lethargy, hind limb paresis, hyperesthesia and cervical ventroflexion have been reported in cats. Anorexia is an early sign.

Treatment:

- Acute exposure
    - Decontamination:
        - Dermal exposure- washing.
        - Oral exposure- emesis, lavage and activated charcoal.
    - Atropine is the antidote for muscarinic signs; it has no effect on nicotinic and central signs. If severe or life threatening muscarinic signs (cyanosis, bradycardia, bronchial secretions) are present, the use of atropine is definitely indicated. An initial anaesthetic dose of 0.02mg/kg can be administered as an atropine response test if there is any uncertainty about the diagnosis. Rapid resolution of suspected muscarinic signs at this dose of atropine indicate that OP or carbamate toxicity is unlikely. Atropine doses of up to 0.1-0.5mg/kg can be administered slowly (1/4 slow IV; remainder IM if required) to effect in confirmed cases until cyanosis, dyspnoea, salivation and bradycardia are resolved. Lower doses are generally required in carbamate toxicity and because of the short half life of carbamate toxicity repeat doses of atropine are unlikely to be required. With OP toxicity higher and repeated doses are frequently required.
    - Atropine frequently causes gut stasis (delaying gastrointestinal transit times) and this should be taken into account when treating orally ingested OP's and carbamates with minimal muscarinic signs.
    - Pralidoxime (2-PAM) acts to reactivate phosphorylated cholinesterase and is indicated for severe nictonic signs of OP toxicity. The dose is 10-20mg/kg up to three times daily. It can be administered SC, IM or slow IV. Atropine should be co-administered with 2-PAM.
    - 2-PAM has anticholinesterase properties and can cause clinical signs of OP toxicity if used when OP toxicity is not present or when the OP has become permanently bound to the AchE and can no longer be dislodged by the 2-PAM. In carbamate toxicity there is a potential risk that administration of 2-PAM may worsen clinical signs which is definitely the case with carbaryl toxicity. Diazepam can be administered for seizures if necessary.

- Intermediate syndrome-
    - Supportive care including ventilation can be administered if required. 2-PAM may be useful if given before permanent 'aging' of acetylcholinesterase occurs; however, there have been anecdotal reports of death in cats.
- Chronic toxicity
    - For organophosphate induced delayed neuropathy treatment involves removal of the source of OP's and supportive care.
    - Diazepam should not be used as an appetite stimulant in cats suffering from chronic toxicity as it has occasionally been associated with the development of muscle tremors and muscarinic signs. The mechanism for this is unknown.

Diagnosis:

- Known contact with toxin and appropriate clinical signs are compatible with the diagnosis.
- Whole blood cholinesterase activity less than 25% of normal can be diagnostic. Values less than 50% of normal are suspicious in both acute toxicity and intermediate syndrome. Normally measured on heparinised whole blood, reference levels are specific to the laboratory. Sample handling and transport should be confirmed with the laboratory. Cholinesterase activity testing can be problematic in carbamate toxicity, due to the short half-life of carbamate binding to cholinesterase; the cholinesterase activity may normalise during transport. .
- Gastric contents can be tested for the specific toxin in acute ingestions.
- An atropine response test can be used in suspected cases of acute OP or carbamate toxicity; 0.02mg/kg atropine is given IV; if muscarinic signs resolve and mydriasis and tachycardia develop then acute OP or carbamate toxicity is not present and no further atropine should be administered.

Prognosis:

- Acute toxicity: - good if the patient survives the initial toxicity. Potential complications include aspiration pneumonia, intussusceptions and the side effects of heat stroke if severe hyperthermia develops.
- The prognosis for intermediate syndrome and OPIDN appears to be good if appropriate supportive care is provided but weeks of support may be required for OPID and ventilation may be required for severe cases of intermediate syndrome.

<u>PERMETHRIN</u>

Permethrin is a lipid soluble synthetic pyrethroid, a class of compounds originally derived from chrysanthemum. This is a common toxicity in cats generally resulting from inappropriate topical administration of specific 'spot-on' flea products or rinses by owners. Secondary exposure may occur in cats which are in close contact with treated dogs or environments. Pyrethrins can also be found in medicated shampoos, some flea collars, and environmental insecticidal treatments. Significant exposure in cats may also occur due to oral ingestion by grooming behaviour. Other synthetic pyrethroids cause similar clinical effects.

Mechanism of action:

- Pyrethroids can slow both opening and closure of voltage sensitive sodium channels, interfering with depolarisation of nerves and resulting in repetitive nerve discharges or prolonged

depolarisation. Motor and sensory nerve fibres are affected, and the lipophilic character of the compounds encourage accumulation and persistence in neural tissues.
- Cats may have increased susceptibility due to deficiencies in hepatic glucuronidation, which slows initial detoxification of these compounds.
- The minimal toxic dose is unknown; toxicity in cats has been seen even with exposure to small amounts.
- Hypothermia may exacerbate the clinical effects of permethrin.

Clinical signs:

- Almost all exposed cats will become symptomatic, and the majority of these will display muscle tremors.
- Common clinical signs include muscle fasciculations, ear twitching, paw flicking, tremors, ataxia, seizures, hyperthermia, and mydriasis.
- Effects on sensory nerves can result in hyperaesthesia and hypersalivation (which may also be seen after oral exposure).
- Clinical signs develop within 3 to 72 hours post exposure.
- Recovery takes from 2 to 3 days on average but up to 5 to 7 days has been reported.

Diagnosis:

- Classic clinical signs are suggestive and owners should be questioned about exposure to flea treatments (either directly on the cat, or on other animals in the household).
- Cats have been reportedly exposed by licking empty packets of spot-on products.

Treatment:

- Decontamination: for dermal exposures wash cat with warm water and hand dishwashing liquid. Avoid hypothermia after bathing.
- Prevent absorption: Activated charcoal is only indicated in confirmed oral exposures as permethrin undergoes minimal enterohepatic recirculation (although other pyrethroids may be more extensively recirculated).
- Prevent hypothermia, which may exacerbate clinical signs by enhancing intracellular sodium movement.
- Management of tremors/seizures*:* The aim of drug therapy is to stop all seizure activity and decrease muscle tremors and fasciculations to a level which is unlikely to result in hyperthermia or muscle damage. Attempting to stop all muscle tremors with drug therapy may result in unnecessarily deep sedation/anaesthesia and respiratory depression.
    - Methocarbamol is a centrally-acting muscle relaxant and very efficacious for muscle fasciculations secondary to permethrin toxicity.
        - Initial dose is 44 – 220 mg/kg IV, given in small boluses of 30-40 mg/kg until tremors have improved or ceased. Methocarbamol is stated to have a maximum 24-hour dose of 330 mg/kg for cats and dogs.
        - If injectable methocarbamol is unavailable, it may be administered PO, or the tablets may be ground up, dissolved in water, and administered per rectum at the same doses used for IV.
    - GABA agonists: both benzodiazepines and Phenobarbital (phenobarbitone) may be used to attenuate clinical signs of tremors or seizures in combination with or instead of methocarbamol.

        - Benzodiazepines (diazepam) may be administered initially as IV bolus doses of 0.25 – 0.5 mg/kg, and may also be administered as a CRI of 0.2 – 0.5 mg/kg/hr
        - Phenobarbital should be administered in small doses of 2-4 mg/kg IV or IM as necessary, not to exceed 16 mg/kg/day.
    - If necessary, propofol or alfaxalone CRI or gas anaesthesia may be used to anesthetize the patient. Neuromuscular blocking agents are not indicated.
- IV fluid therapy to maintain hydration if the animal is unable to drink.
    - More aggressive fluid rates may be indicated in the presence of myoglobinuria to minimise the possibility of myoglobinuria-induced nephropathy.
    - Measurement of blood electrolytes will help to guide additional fluid therapy and choices (see section 4 chapter 3)
- The highly lipophilic nature of the pyrethroids suggests that intravenous lipid administration may be an effective therapy to decrease severity and duration of clinical signs.

Prognosis:

- Good unless clinical signs have been present for a prolonged period prior to instituting appropriate treatment; intensive supportive care may be necessary. Treatment delays or the presence of generalised seizures is associated with a worse prognosis and increases the likelihood of death.
- Death has been reported to occur in 5-37% of cases.

Metabolic Encephalopathies

Metabolic encephalopathy (ME) is a clinical syndrome resulting from disorders of metabolism. ME is characterized by altered mental state and neurological deficits due to disruption of brain function and structure secondary to energy deprivation, derangements of electrolytes, acid-base balance or accumulation of endogenous toxins. ME is not a single entity but a heterogeneous and frequently multifactorial condition. It is commonly encountered in the critical care setting and arises secondary to conditions such as liver dysfunction, endocrinopathy or renal failure. Endogenous metabolic diseases due to inborn errors of CNS metabolism also occur occasionally.

Metabolic encephalopathies typically cause diffuse, symmetrical forebrain signs. Onset may be acute or chronic and signs may wax and wane. The earliest and most consistent signs are depression of consciousness and generalised seizures. Other neurological signs vary with the type and severity of the metabolic disturbance.

Common *historic* signs
Waxing and waning neurologic signs / behaviour change
Temporal relationship between feeding and neurological signs
Seizure activity
Altered mentation
Blindness
Gastrointestinal signs
Increased or decreased appetite
Pica
Dermatologic signs i.e., alopecia
Tremor

Common *clinical* signs of metabolic encephalopathies
Predominant forebrain signs (and/or brainstem)
Seizures
Behaviour change: aggression, anxiety, dementia, mania
Obtundation/stupor/coma
Blindness with normal pupillary light reflexes (amaurosis)
Symmetrical neurological deficits

The key to successful treatment in these patients is:

1) Rapid identification of underlying causes

2) Rapid treatment of metabolic abnormalities

3) Effective monitoring to rapidly identify potentially life-threatening abnormalities.

4) Effective symptomatic treatment is frequently the difference between success and failure

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a complex neurological condition that occurs as a consequence of acute or chronic liver disease most frequently due to congenital portovascular anomalies, hepatic microvascular dysplasia or liver failure of any cause including intoxication or infection. HE is well-documented in both humans and small animals and is characterised by changes in behaviour, consciousness and neuromuscular function. Neurological signs may include head-pressing, hyper-reflexia, rigidity, myoclonus, seizures and coma. Signs of hepatic dysfunction (weight loss, polydipsia, anorexia and vomiting) may be present. Ptyalism is another common sign especially in cats. Multiple pathophysiologic theories have been proposed and are briefly discussed here.

Ammonia: Elevated serum ammonia is characteristic of HE but the role of ammonia in the pathogenesis of hepatic encephalopathy is controversial since the degree of correlation between HE severity and blood ammonia concentration is variable. The labile nature of plasma ammonia may be the origin of much of the inconsistency in results obtained. Ammonia (NH_3) is produced primarily in the gastrointestinal tract by bacterial metabolism of amino acids, urea and glutamine. Ammonia diffuses through the intestinal mucosa into portal blood and is delivered to the liver as ammonium (NH_4^+) (Figure 3). The liver itself produces ammonium ions from amino acid deamination. In liver failure, hepatic ammonia detoxification is ineffective leading to hyperammonaemia. Ammonium ions are detoxified predominantly in the liver via the urea cycle with resultant production of glutamine. The brain lacks a urea cycle and relies on production of glutamine for detoxification of ammonia which is a direct neurotoxin acting via chloride channel inhibition. It has been suggested that the glutamine produced acts as the “Trojan Horse” of HE pathogenesis by inducing oxidative stress. Much of the evidence supporting the ammonia theory comes from the apparent efficacy of anti-ammonia therapies such as lactulose, oral synbiotics, oral antimicrobials and enteral or parenteral L-ornithine-L-aspartate.

Diagnosis: HE is diagnosed primarily by clinical signs in conjunction with biochemical evidence of liver dysfunction. Serum biochemistry evidence of liver dysfunction includes hypoalbuminaemia, hypocholesterolaemia, low BUN, and hypoglycaemia. Increased liver enzyme concentrations indicate hepatocellular damage or cholestasis which are commonly seen in patients with disease processes causing liver dysfunction. Patients with congenital portovascular anomalies commonly have two to threefold increases in liver enzymes. Supportive findings from specific liver function tests include hyperammonaemia, increased pre and/or post-prandial bile acids or clotting time prolongations. Microcytosis is an inconsistent haematological finding in liver disease. Abdominal imaging and in

particular ultrasound may be useful in identifying liver pathology such as biliary tract disease or neoplasia. Identification of a portosystemic shunt is possible by ultrasonography or mesenteric portography. Magnetic resonance imaging may reveal cortical atrophy characterised by widened sulci, and hyperintensity of the lentiform nuclei on T1 weighted images. Hepatic biopsy is rarely required.

Treatment:

HE therapy has three aims:

- Stop seizures
- Reduce serum levels of neurotoxic metabolites
- Treat underlying cause

Stop seizures

If the patient is having seizures, antiepileptic drug treatment will be necessary. Controversy exists over the use of benzodiazepines for treatment of HE associated seizures, however they remain our first-line drug of choice. For maintenance therapy, ideally, a drug with no effect on hepatic metabolism should be used. Potassium bromide is theoretically a good choice which can be given via a loading protocol over 1-6 days either orally or rectally. Levetiracetam (20-60mg/kg) may be effective when given intravenously or per rectum although it has not yet been evaluated for efficacy in animals via these routes or at these doses. In patients with status epilepticus secondary to HE, it may be necessary to use anaesthetic drugs, some of which have potent anti-seizure properties, in order to terminate seizure activity. Propofol (1-4mg/kg for induction, given to effect followed by CRI 0.1-0.6mg/kg/min) can be used for this. Once anaesthesia is induced patients must be intubated to protect their airway and an intensive protocol of monitoring and care of the recumbent patient initiated. It should be noted that electrical seizure activity may continue despite the appearance of a cessation of tonic or clonic activity. Other measures to treat HE must also be initiated in patients with status epilepticus.

Reduce neurotoxic metabolites

Oral lactulose (0.5-1ml/kg PO q8h) decreases gut transit time, helps to prevent constipation and alters gut flora reducing colonic ammonia production. Once metabolised it produces an acid environment trapping ammonia as ammonium. In stuporous or comatose patients lactulose can be administered by retention enema 20ml/kg (made of three parts lactulose diluted in seven parts warm water) q 4-6 hours.

Ampicillin (22mg/kg PO q8h) or if unavailable metronidazole (7.5mg/kg PO q8h) or neomycin (20mg/kg PO q8h) can be used to reduce urea-splitting colonic bacterial numbers. Proximal gastrointestinal haemorrhage may exacerbate encephalopathic signs and should be treated with proton-pump inhibitors such as omeprazole. This drug can be given orally or intravenously (1mg/kg). Additionally, gastrointestinal bleeding in patients with liver dysfunction must be investigated to identify any underlying thrombocytopenia or coagulopathy that requires specific treatment.

If appropriate based on the patient's mentation the diet may be altered to a high quality, low quantity protein to reduce ammonia production in the GI tract. Care must be taken not to excessively limit protein intake since many patients with portovascular anomalies are young, growing patients and such protein-restriction may be detrimental to their musculoskeletal development.

Treat underlying cause

Surgical ligation of single, uncomplicated extrahepatic or intrahepatic shunts is the most direct treatment. Dogs and cats with multiple extrahepatic shunts and those with acquired shunts secondary to cirrhosis or acute fulminant hepatic failure are not candidates for surgery. In case of acquired liver disease, specific therapy for any underlying cause should be instituted.

Prognosis: The prognosis for dogs and cats with HE is dependent upon the degree of hepatic impairment and the severity of the neurological signs. It is guarded in patients with seizures secondary to HE; poor in patients with liver failure; and fair with surgical treatment in patients with portovascular anomalies.

Sodium disorders

Most disorders of sodium concentration result from disorders of water balance. Both hyper- and hyponatraemia can cause neurologic dysfunction via alterations in neuronal cell volume and function. Slow, gradual alterations in sodium concentration are well tolerated until concentrations become extreme. Small absolute changes which occur rapidly may cause more profound neurologic dysfunction than larger more gradual alterations.

Hypernatraemia

Blood sodium levels reflect the ratio of sodium to water in the extracellular fluid and account for most of the osmotically active particles in serum. Hypernatraemia is indicative of a relative increase in total body sodium relative to total body water. It occurs secondary to net solute gain, sodium-free water loss or hypotonic fluid loss. Causes of hypernatremia include:

- Net solute gain: excess salt intake associated with salt poisoning, administration of IV hypertonic saline or sodium bicarbonate. Water loss and salt gain can also occur with hyperaldosteronism and hyperadrenocorticism
- Sodium-free water loss: diabetes insipidus, primary hypodypsia, water unavailable or patient unable to drink, or heat stroke.
- Hypotonic fluid loss: gastro-intestinal loss (vomiting, diarrhoea, small intestinal obstruction), third space loss (pancreatitis, peritonitis), osmotic diuresis (mannitol infusion, hyperglycemia), chemical diuresis (furosemide), nonoliguric renal failure, chronic renal failure, post-obstructive diuresis

Hypernatremia can be further divided into hypovolemic (hypotonic loss), normovolemic (sodium-free water loss) and hypervolemic (net solute gain) form. Hypernatremia due to a gain of sodium results in increased extracellular fluid (ECF) (hypervolemic hypernatremia). Pure water loss results in relative preservation of ECF (normovolemic hypernatremia) while hypotonic fluid loss results in decreased

ECF volume (hypovolemic hypernatremia). With the latter, affected patients are therefore more likely to show signs of volume depletion (tachycardia, increased capillary refill time, weak pulse). Evaluation of the volume status of the patient is therefore important in the process of identifying the underlying cause of hypernatremia and treatment approach.

The increase in serum sodium creates a hypertonic state in the extracellular fluid. Hypernatraemia leads to cell shrinkage secondary to osmotic water movement into the hyperosmolar interstitium. The decrease in brain volume caused by cellular dehydration can cause tearing of small intracranial blood vessels and haemorrhage (subarachnoid, subdural and/or intraparenchymal). Cells of the CNS are very intolerant of such volume changes leading to clinical signs including obtundation, head pressing, seizures, ataxia, tremors, blindness and coma. In addition, signs of volume depletion are often present in hypernatremia secondary to hypotonic fluid losses while signs of hypervolemia (e.g. pulmonary edema) may be present in case of net solute gain. Clinical signs typically develop if the sodium concentration alters at a rate >1mEq/l/hr or if the absolute sodium concentration exceeds 180mEq/L (180 mmol/l). If sodium concentrations alter slowly, the brain adapts by producing idiogenic osmoles such as taurine, sorbitol and inositol. These molecules increase intracellular osmolality, buffering cell volume against the increased extracellular sodium concentration. Rapid correction of chronic hypernatraemia (>0.5-1mEq/L/hr) can lead to osmotic gradient reversal, inducing water to move into cells causing cell swelling, cerebral oedema and clinical signs of intracranial hypertension.

Treatment of hypernatraemia
• Identify and treat both underlying cause and sodium abnormality. • There is no standard method of correction to suit all, treatment should be individualised aiming to replace the water deficit and treat the underlying cause. • Correction of sodium concentration should occur at the same rate at which it developed – i.e. rapid in cases of salt intoxication; slowly in cases of fluid loss. • Rate of blood sodium change should not exceed 0.5-1mEq/L/h. • If serum sodium concentrations are lowered too quickly, cerebral oedema may result with clinical deterioration in consciousness • Monitor blood sodium concentration every 4-6 hours during correction.

<u>Treating hypernatraemia secondary to fluid loss</u>

- A hypovolaemic, hypernatraemic patient should be volume resuscitated with a fluid containing a sodium concentration equal to that of the patient. This can be created by adding aliquots of a concentrated NaCl solution such as 7.2% saline (1.23mEq NaCl per ml) to an isotonic replacement crystalloid solution such as 0.9% saline or Hartmann's solution.
- For example, a patient with a plasma sodium concentration of 181mEq/l will need a solution which contains 181mEq/l NaCl (equivalent to a 1.06% solution). This can be prepared by increasing the sodium concentration of 0.9% saline (154mEq/l) by adding 27mEq of NaCl. This is achieved by adding 22ml of 7.2% saline to 1000ml of 0.9% saline. Be aware that

1000ml fluid bags typically contain an excess of 20ml which will need to be removed prior to addition of the 7.2% saline. The sodium concentration of the resultant solution should be checked using an electrolyte analyser prior to bolus administration to the patient.

- Following volume resuscitation, the hypernatraemic patient's free water deficit should be replaced slowly to reduce sodium concentration at a rate of 0.5-1mEq/L/hr. If a recent bodyweight is not available the following equation can be used to approximate the free water deficit:

$$Free\ water\ deficit\ (L) = 0.6 \times Bodyweight\ (kg) \times \left(\frac{Measured\ [Na^+]}{Normal\ [Na^+]} - 1\right)$$

- The predicted change in blood sodium concentration from administration of one litre of fluid can be calculated using the following equation:

$$Change\ in\ [Na^+] = \frac{Infusate\ [Na^+] - Blood\ [Na^+]}{\left((Bodyweight\ (kg) \times 0.6) + 1\right)}$$

- Free water replacement can be achieved with a range of fluids. If significant ongoing losses such as diarrhoea are occurring use of 0.9% saline or Hartmann's solution will be safer. Hypotonic fluids such as 0.45% saline or 5% dextrose in water can be used if ongoing losses are minimal. Hypotonic fluids will reduce the sodium concentration more rapidly than an equal volume of isotonic fluid (see section 4 chapter 3 for further details).

<u>Treating hypernatraemia secondary to sodium gain</u>

- With hypernatraemia patients are typically hypervolaemic, may have elevated systemic blood pressure and are at risk of pulmonary oedema.
- Furosemide at 1-2mg/kg IV will facilitate loss of both sodium and excess fluid.
- 5% dextrose in water can be used to correct the sodium concentration. Should the sodium concentration drop more rapidly than >0.5 mEq/L/h this may need to be altered to 0.45% saline or Hartmann's solution.
- Frequent [Na^+] monitoring will guide use of furosemide and fluid therapy.

Hyponatraemia

Hyponatraemia occurs primarily due to loss of salt, gain of water, gain of hypotonic fluid or addition of hypertonic solution with sodium (glucose or mannitol).

Aside for hyperglycemia and mannitol administration that may lead to hyponatremia and hyperosmolality, most hyponatremic patients are hypo-osmolar. Hyponatremia with low plasma osmolality may be accompanied by normal (syndrome of inappropriate ADH secretion or SIADH,

psychogenic polydypsia, hypotonic fluid infusion), decreased (Addison's disease, gastrointestinal and third space loss), or increased plasma volume (congestive heart failure, severe liver disease, nephrotic syndrome, advanced renal failure). As for hypernatremia, determination of the volume status of the patient is essential in the process of identifying the underlying cause of hyponatremia and treatment approach.

Mild to moderate hyponatraemia is typically occult. Severe hyponatraemia where sodium concentrations are less than 120mEq/L (120 mmol/l) or rapid decreases in sodium concentration (>1mEq/l/hr) are associated with obtundation, head pressing, seizures and coma. In addition, hypovolemic hyponatraemic patients may have signs of dehydration and hypovolemia (e.g. rapid and weak pulse, hypotension, cold extremities, prolonged capillary refill time) while hypervolemic patients may be presented with ascites, pulmonary oedema, peripheral oedema or jugular distension.

Hyponatraemia leads to cell swelling and cerebral oedema secondary to osmotic water movement into cells. A gradual change in sodium concentration allows cells to adapt by expelling intracellular solutes to decrease intracellular osmolality and restore normal cell volume. Rapid correction (>0.5-1mEq/L/hr) of hyponatraemia can cause severe cell shrinkage as water moves into the increasing osmolality of the extracellular environment. This shrinkage can separate the neurons from their myelin covering leading to myelinolysis. In humans this occurs predominantly in the pons (central pontine myelinolysis; also known as osmotic demyelination syndrome) whilst in dogs it occurs principally in the thalamus (Fig. 1).

Treatment of hyponatraemia

- Identify and treat both underlying cause and sodium abnormality.
- Hyponatraemia almost always develops slowly; therefore, hyponatraemia must be corrected **slowly**, to avoid life-threatening neurological damage (osmotic demyelination syndrome) which may take several days to become evident.
- Monitor sodium every 4-6 hours during correction.
- Hypovolaemia should be corrected with 0.9% saline
- Do not correct [Na^+] at a rate >0.5mEq/L/hr.
- Hypertonic saline is rarely required for treatment of hyponatraemia
- Hypoperfused patients may be depressed – do not confuse this with neurological signs of hyponatraemia e.g. seizures, coma
- Treat seizures due to Na^+ abnormalities with 0.5mg/kg diazepam IV or per rectum

Hypothyroid myxedema coma

Myxedema coma is an extreme life-threatening form of canine hypothyroidism. Patients with this rare endocrine emergency may present with mental dullness, stupor or coma. In dogs, typical clinical signs

include obesity, oedema, mental dullness, hypothermia, bradycardia, hypotension and hypoventilation. Stupor and coma are less common. Cranial nerve dysfunction (especially facial and vestibular) can also be noted. Myxedema coma pathophysiology is incompletely understood. Dobermann Pinschers seems to be over-represented. Thyroid hormones indirectly regulate multiple cell functions affecting catabolism, metabolism and development. Thyroid hormones also play permissive roles in multiple organ systems. The altered mental status in this condition results from direct effects of reduced thyroid hormone concentrations, and indirectly from decreased cerebral blood flow, cerebral oedema and hyponatraemia. Myxedema coma is typically precipitated by an event which overwhelms normal homeostasis such as infection, concurrent administration of thyroid hormone-altering medication or surgery, although in dogs no single event has been repeatedly identified.

Diagnosis: Identification of profoundly low serum thyroxine levels (or free thyroxine levels by equilibrium dialysis) ± increased thyroid stimulating hormone (endogenous TSH) levels assists with diagnosis. Interference from intercurrent disease must be considered when interpreting thyroid function tests in sick patients. Blood gases may reveal hypoxaemia and hypercarbia. Patients may be hypoglycaemic and have other biochemical changes consistent with hypothyroidism e.g. hypercholesterolaemia, hyponatraemia. Electrocardiography may identify bradyarrhythmias, and response to treatment may actually aid in diagnosis. Investigation must also be directed toward identifying a predisposing cause such as infection, recent drug therapy or heart failure.

Treatment:

- Assess respiratory status. Provide oxygen and ventilatory support if required.
- Warmed intravenous fluid therapy ± supplementary glucose as appropriate.
- Passive external rewarming.
- L-thyroxine 1-5µg/kg IV q12h. Resolution of abnormal mentation, ambulation, and systolic hypotension should be expected within 30 hours. Injectable levothyroxine may not be readily available, in which case, oral levothyroxine may be administered via an orogastric tube. A liquid preparation is available and may be sourced from a local hospital. Care must be taken to avoid aspiration if the patient is obtunded or stuporous.
- Serum thyroxine levels should be monitored daily and oral levothyroxine begun once serum thyroxine levels are normal and appetite has resumed. This may take several days.

Prognosis: Guarded. Poor if intercurrent disease also present.

HYPOGLYCEMIA

Hypoglycaemia may arise from numerous conditions. Hypoglycaemic neurologic dysfunction has been reported in patients with endogenous and iatrogenic hyperinsulinaemia, sepsis, liver failure, portosystemic shunting, hypoadrenocorticism, neoplasia (insulinoma or extrapancreatic insulin-like producing neoplasm), neonatal hepatopathy and xylitol toxicity. Hypoglycaemic neurologic dysfunction is also reported in toy breeds and in hunting dogs.

Despite constituting only 2% of total body mass, the brain utilizes 25% of total body glucose due to its inherently high metabolic rate and limited local storage. Brain interstitial glucose concentrations are typically 20-30% less than plasma; hence glucose must be continuously transported into the brain. Blood glucose is closely monitored by glucose sensing neurons in the hypothalamic ventromedial nuclei. Hypoglycaemia stimulates these neurons leading to increased sympathetic output and hence increased plasma epinephrine (adrenalin), norepinephrine (noradrenalin), cortisol, glucagon and somatostatin concentrations. These counter-regulatory hormones act to increase plasma glucose concentration, increase glucose delivery to and uptake by the brain and alter glucose metabolic pathways. Insulin is not required for glucose uptake by the brain because of specific glucose transporting transmembrane proteins (GLUTs).

Clinical signs of cortical neuronal damage range from hyperexcitability to tremors, blindness, cognitive dysfunction, seizures, coma, and death. Nervousness, tremors and weakness typically appear when plasma glucose levels approach 3.6-3.8mmol/L (65.4-69.1mg/dl). When plasma glucose levels fall below 1mmol/L (18mg/dl), seizures, severe brain damage, coma and death may occur. However, as with many homeostatically controlled parameters the rate of change may be more important than the absolute values in determining the point of onset and severity of clinical signs. Early recognition and therapy for hypoglycaemia is vital both for early return of neuronal function and to diminish the risk of permanent damage.

Diagnosis: Blood glucose measurement which is consistently less than the reference interval is diagnostic of hypoglycaemia. Beware of false hypoglycaemia resulting from use of human point-of-care glucometers in haemoconcentrated patients. Falsely low glucose values may also result from delay separation of serum from red blood cells (RBC) as RBC continue to consume glucose for glycolysis. This can be prevented by using sodium fluoride tube. Once hypoglycemia is identified, a thorough investigation for an underlying cause must be undertaken. Principle rule-outs include: sepsis, liver failure, hypoadrenocorticism, insulin overdose, xylitol toxicity, neonatal or toy-breed hypoglycaemia, insulinoma and other paraneoplastic hypoglycaemias.

Treatment:

- Address underlying cause of hypoglycemia
- Intravenous dextrose bolus: 0.5g/kg 50% dextrose diluted 1:4 with 0.9% saline.
- Continue with a constant rate infusion of 2.5-5% dextrose in an isotonic fluid as required to maintain euglycaemia. Solutions of 2.5-5% dextrose can be readily prepared by adding

aliquots of a solution of 50% dextrose to 0.9% saline or Hartmann's solution e.g. 50ml of 50% dextrose in 500ml saline creates a 5% solution.

- Administer glucose syrup orally if intravenous access is not available. Be cautious using the oral route if patient is actively seizing.
- Feed frequent small meals throughout the day.

THIAMINE DEFICIENCY

Vitamin B1 (thiamine) is an essential dietary component in small animals. Thiamine pyrophosphate is a coenzyme for pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase, all of which are involved in carbohydrate metabolism. Thiamine deficiency impairs oxidation of ketoacids leading to impaired cerebral energy metabolism, focal lactic acidosis, NMDA receptor mediated excitotoxicity and blood-brain barrier breakdown. Thiamine deficiency, termed Wernicke's encephalopathy in people, causes polioencephalomalacia with bilaterally symmetrical spongiosis, necrosis and brainstem nuclei haemorrhage. Thiamine deficient dogs present with dilated unresponsive pupils and mild ataxia progressing to altered mentation, hyperaesthesia, tetraparesis, seizures and opisthotonus. Cats in contrast display central vestibular signs, head tremors, mydriasis and cervical ventroflexion. Thiamine deficiency in dogs and cats has been reported secondary to feeding of sulphur dioxide preserved meat, feeding thiamine deficient diets or fresh fish diets containing thiaminase. Thiamine deficiency can occur due to decreased intake, impaired absorption due to intestinal disease, liver dysfunction, increased utilisation secondary to fever or infection or increased urinary loss.

Diagnosis: Diagnosis of thiamine deficiency is typically made on the basis of signalment, clinical signs and a detailed dietary history. Confirmation of the deficiency can be made by assays of thiamine metabolites in blood or by measurement of erythrocyte transketolase activity. Presumptive diagnosis can be made on the basis of urinary organic acid profile analysis. Occasionally a diagnosis is only confirmed postmortem. Clinical sign resolution following treatment with thiamine is supportive of the diagnosis. CSF analysis does not appear to be discriminatory for thiamine deficiency. Magnetic resonance imaging findings have been described in the dog and cat including non-contrast enhancing bilaterally symmetrical thalamic and brainstem nuclear hyperintensity evident on the T2-weighted and FLAIR images.

Treatment: Thiamine deficiency can be treated with thiamine hydrochloride (5-50mg/dog IV q24h or 1-20 mg/cat by slow CRI). The underlying disorder should also be investigated and managed appropriately.

Prognosis: Provided the diagnosis is made early or presumptive treatment is rapidly initiated then the prognosis for thiamine deficiency is good.