**Supporting the intoxicated patient: toxicants affecting the gastrointestinal and hepatobiliary systems**

**Background:** The gastrointestinal and hepatic systems are the first to encounter many potentially toxic substances. Recognition, stabilisation and treatment of the consequences of intoxication are key to successful management.

**Aim of the article:** This final article in the series of four will focus on toxicants that affect the gastrointestinal or hepatobiliary systems, outlining the aetiology of the clinical signs observed, along with diagnostic assessment and treatment considerations.

Previous articles in this series have highlighted the approach to decontamination of the asymptomatic patient exposed to a toxicant (Humm and Greensmith 2019), toxicants affecting the neurologic and cardiovascular systems (Tinson and Cook 2020) and haematologic and renal systems (Humm and Tinson 2020). This article focusses on toxicants that affect the gastrointestinal or hepatobiliary systems. As recommended previously, when managing intoxicated patients, contact with the Veterinary Poisons Information Service ([www.vpisglobal.com](http://www.vpisglobal.com)) is advised to allow discussion on a case-by-case basis.

#### **Key learning outcomes**

**After reading this article, you should understand:**

* Basic pathophysiological mechanisms behind the common hepatic and gastrointestinal toxicants seen in veterinary practice;
* How to recognise patients that have been affected by hepatic and gastrointestinal toxicants;
* The approach to stabilisation and treatment of patients affected by hepatic and gastrointestinal toxicants;
* Recommended drug therapy in patients with hepatic and gastrointestinal dysfunction.

**Toxicants affecting the gastrointestinal system**

**Major body systems**

As always, initial consideration should be given to the major body systems before specifically addressing gastrointestinal clinical signs. Gastrointestinal clinical signs are likely to progress without stabilisation of, for example, systemic perfusion and oxygen delivery.

**Laboratory findings**

Many laboratory test results in cases with gastrointestinal intoxications will be non-specific, if present at all. For this reason, they are likely of more benefit for monitoring rather than diagnostic purposes. For example, patients with large volumes of gastrointestinal fluid losses have the potential to be volume deplete and haemoconcentrated. Acid-base disorders may be appreciable; large volume diarrhoea can result in excessive bicarbonate loss with resulting acidosis, while metabolic alkalosis can develop with excessive vomiting. Electrolyte derangements are common and, as with any critically ill hospitalised patient, a basic daily assessment including packed cell volume, total solids, sodium, potassium and chloride is advisable.

**General approach and stabilisation**

Many toxicants are associated with gastrointestinal symptoms, and often the clinical signs are self-limiting and self-resolving. To that end, an important consideration in managing gastrointestinal symptoms that are suspected to be due to intoxication, is knowing when treatment is even indicated. For this reason, we will briefly consider a generalised approach to the patient with gastrointestinal dysfunction after an intoxication, focusing on some important considerations.

Clinical presentation will vary widely, but severe gastrointestinal dysfunction can be life-threatening and remotely affect multiple organ systems; hence the required approach is multifaceted. Enteral nutrition should begin as soon as the patient is tolerant as it affords improvement in mucosal barrier health, mucus production and bicarbonate secretion. If regurgitation is present, the cause should be ascertained (i.e. oesophagitis, or as a consequence of gastrointestinal stasis with gastric distension). Oesophagitis is managed supportively (e.g. analgesia, gastric acid suppressants, antacids) but gastrointestinal stasis may necessitate prokinetics such as metoclopramide, cisapride and/or erythromycin – (see table 1), with or without nasogastric intubation for decompression and delivery of nutrition. Nausea is often seen in patients with regurgitation or vomiting and these animals may benefit from antiemetics such as maropitant and anti-nausea medications such as ondansetron. Aspiration is not uncommon in these patients which may cause transient pneumonitis (for which antibiotics may not be necessary), or an established pneumonia.

Adequate analgesia is usually provided by opioids, and this is important as pain can contribute to recumbency, immunosuppression and gastrointestinal stasis. Provision of analgesia outweighs the possible contribution to gastric stasis in opioid use. Gastrointestinal dysfunction can increase vagal tone and lead to bradycardia; this does not tend to require treatment but should be targeted with anticholinergics (i.e. atropine) if a vagally mediated cardiopulmonary arrest occurs or is suspected.

Early mobilisation (including passive range of motion, targeted physiotherapy, and assisted standing and walking) is also important if the patient is recumbent; it promotes gastrointestinal motility, prevents pressure sores, encourages mucociliary clearance and effectual coughing, and is associated with improved outcomes.

# There is growing evidence of the benefit of probiotics in treatment (Ziese and others 2018) and avoidance (Rose and others 2017) of diarrhoea in dogs so their use should be strongly considered.

**Table 1.** details the common gastrointestinal medications and their indications.

For further reading please consult the ACVIM consensus statement on gastroprotectants (Marks and others 2018). 5-HT – Serotonin, Ach – Acetylcholine, NK – Neurokinin.

|  |
| --- |
| **Table 1. Common gastrointestinal medications and their clinical use** |
| **Medication** | **Mechanism of action** | **Notes and clinical use** | **Dose** |
| **Omeprazole** | Inhibition of gastric acid secretion | Justified in high risk or proven ulcerative disease. Use twice daily. Maximal effect achieved after 2-4 days  | 1 mg/kg IV/PO q12h |
| **Misoprostol** | Promotes mucosal blood flow and mucus production | NSAID intoxication. Handle with gloves and not to be handled by pregnant women | 2-7.5 𝜇g/kg PO q8-12h |
| **Ranitidine** | Blocking of parietal cell H2 receptors, impairing gastric acid secretion. | Inferior to proton pump inhibitors (eg. omeprazole) for suppression of gastric acidity. Not prokinetic | 2 mg/kg IV q12h |
| **Maropitant** | NK-1 receptor antagonist, inhibiting substance P | First line anti-emetic | 1 mg/kg SC q24h |
| **Ondansetron** | Central 5-HT3 antagonism | Second line antiemetic, likely with better anti-nausea effect than maropitant | 0.5-1 mg/kg IV q12-24h |
| **Metoclopramide** | Gastrointestinal 5-HT4 agonism (prokinetic) and central anti-emetic via dopaminergic and 5-HT3 antagonism | Gastrointestinal stasis in hospitalised patients or as part of a multimodal anti-emetic plan | 1-2 mg/kg/day as a continous rate IV infusion |
| **Cisapride** | Gastrointestinal 5-HT4 agonism and increase in ACh release in enteric nervous system | First or second line pro-kinetic. Only available in tablet form | 0.1-0.5 mg/kg PO q8-12h |
| **Erythromycin** | Motilin agonist, 5-HT3 antagonist | Likely as effective as metoclopramide but often only available orally in UK. Oral liquid preparation lends to use in small patients | 0.5-1 mg/kg PO q8h |
| **Aluminium hydroxide** | Inhibition of pepsin activity, stimulation of gastric prostaglandin, bile acid binding | Generally not clinically effective: transient effect on gastric pH necessitates prohibitively frequent administration | Empirical. Up to 10ml PO q4h |
| **Sucralfate (aluminium hydroxide plus sucrose octasulphate)** | Inhibition of pepsin activity, local antacid, stimulation of gastric prostaglandin, bile acid binding complexes with protein at damaged mucosal surfaces, local analgesic | May be of benefit in oesophageal injury. Liquid suspension likely more effective than tablet form | 0.25-2g per cat/dog q6-12h |

**Common toxicants affecting GI system**

The VPIS list of the most common intoxications include nonsteroidal anti-inflammatory drugs (NSAIDs) and chocolate, both of which are likely to cause gastrointestinal dysfunction.

**NSAIDS**

# COX-1 and COX-2 induced prostaglandins serve to increase gastric mucosal blood supply and mucus production, and promote mucosal healing, respectively. Whether non-specific or COX-2 selective, all NSAIDs will impair both COX-1 and COX-2 enzymes to some degree. Gastrointestinal side effects (such as vomiting, diarrhoea and anorexia) are the most common adverse effects, even of COX-2 selective NSAIDs (Monteiro-Steagall and others 2013). While meloxicam, carprofen and firocoxib overdoses are common owing to veterinary prescription, ibuprofen and naproxen intoxications are also common due both animal scavenging or ill-informed owner administration as possible causes.

# Gastrointestinal side effects of NSAID use in dogs are unpredictable, and their development should always prompt close monitoring. NSAIDS have been identified as a risk factor for gastrointestinal ulceration (Fitzgerald and others 2017) and spontaneous gastrointestinal perforation, even after single or short term dosing (Cariou and others 2009; Cariou and others 2010; Enberg and others 2006; Runk and others 1999). Whilst ulceration and perforation often occurs at the pylorus and proximal duodenum, it can also occur in the caecum. It is important to recognise that gastrointestinal adverse effects can occur at appropriate doses.

Gastrointestinal symptoms appear to develop before and at lower doses than clinically recognisable acute kidney injury, and a spectrum of clinical signs exists. For example, ibuprofen intoxication has been reported to produce gastrointestinal symptoms between 50-125mg/kg , acute kidney injury above approximately 175mg/kg, and neurological effects (seizures and coma) above 400mg/kg. Gastrointestinal clinical signs often develop within 2 hours, while clinical evidence of acute kidney injury may be delayed by up to 5 days (*BSAVA/VPIS Guide to Common Canine Poisons*, 2012).

**Treatment of NSAID intoxication**

Dogs with NSAID intoxication can present as confirmed, recent intoxication without clinical signs, or after absorption with the development of clinical signs. Emesis and activated charcoal can be employed in the former, but these will not beneficial once clinical signs are apparent. When activated charcoal is indicated, a single dose may be all that is required (Koenigshof and others 2015) but multidosing is commonplace.

# Intralipid therapy has also shown promise in management of naproxen, carprofen and ibuprofen toxicity, and should be considered in patients with recent large dose NSAID intoxication (Bolfer and others 2014; Chumbler and others 2020; Herring and others 2015).

In severe, recent (<12 hours) NSAID intoxications in which renal and CNS impairment is expected or observed, therapeutic plasma exchange (available at some referral centres including the authors’ hospital) should be considered as early as possible. This has been shown to be effective at reducing circulating meloxicam (Walton and others 2017b), ibuprofen (Walton and others 2017a), carprofen (Kjaergaard and others 2018), and naproxen (Kicera-Temple and others 2019), with growing support of its use in severe NSAID intoxications (Rosenthal and Labato 2019).

Misoprostol is a prostaglandin E1 analogue which reduces gastric acidity, promotes mucosal blood flow and mucus production, and preserves epithelial cell junctions. Despite a lack of documented benefit across the entire NSAID class, its use can be justified when gastrointestinal signs are present or expected after NSAID intoxication. Care must be taken however as it is a recognised abortifacient in people; gloves should be used and pregnant people must not handle the drug.

Despite the theoretical indication, proton pump inhibition in NSAID toxicity is a controversial topic. Intestinal dysbiosis secondary to PPI use has the capacity to worsen NSAID induced mucosal injury (Marlicz and others 2014). That said, currently, they are still utilised clinically in NSAID intoxications in people and animals (Marks and others 2018).

Beyond these specific treatment considerations, treatment is largely supportive, paying careful attention to fluid balance, nutrition and the potential for gastrointestinal perforation, for example with frequent point of care ultrasound examinations to monitor for the presence or development of peritoneal fluid.

**Chocolate**

In cases of significant chocolate ingestion it is likely that the patient will vomit of its own accord within the first 6 hours and also develops diarrhoea. Management of the gastrointestinal symptoms is unlikely to require more than antiemetic and intravenous fluid therapy, but occasionally patients will develop pancreatitis and require more intensive treatment. A diagnosis of pancreatitis or concurrent foreign body ingestion should be pursued in any patient with protracted gastrointestinal signs. Please see the second article in this series for management of chocolate associated cardiovascular compromise (Tinson and Cook 2020).

**Battery ingestion.**

While in many cases of battery ingestion the patient will remain asymptomatic and the battery passes without complication, usually within 2 days (Bates and others 2016), batteries can cause life threatening ulcerative lesions if they become lodged and this is a particular risk with button cell batteries. Emesis should not be attempted due to the risk of the battery becoming lodged in the oesophagus, necessitating emergency endoscopic retrieval. Radiographic monitoring is advised, especially when clinical signs develop, in case the battery has caused an obstruction or is leaking (for example having been partially chewed) and therefore requiring removal.

**Digoxin**

Digoxin is a cardiac glycoside predominantly utilised for the treatment of supraventricular tachycardias such as atrial fibrillation. Owing to Na+/K+ ATP-ase inhibition, gastrointestinal side effects including vomiting, diarrhoea and anorexia are common with both chronic dosing and acute toxicity. In acute and recent ingestion, if there are no CNS signs such as altered mental status or seizures, then emesis should be induced. Considering its mild lipophilicity, intralipid may be useful in acute intoxications. Repeated doses of activated charcoal are recommended due to enterohepatic recirculation. DigiFab® is available in severe intoxications but may be prohibitively expensive (approaching £1000 per vial).

**Gastrointestinal plant intoxications**

There are too many plants with gastrointestinal toxicity to cover in this article so please consult the BSAVA/VPIS Guide to Common Canine and Feline Poisons for further information. Importantly, many free applications for remote plant identification using photographs of leaves, flowers and fruits now exist, and these can prove extremely useful for diagnostic and prognostic purposes. Some of the most common toxicants are discussed below.

**Mistletoe (*Viscum album*)**

Mistletoe ingestion is likely to cause vomiting, diarrhoea, hypersalivation and weakness within 2-3 hours of ingestion. There is no need to decontaminate and supportive care is all that is required.

**Conkers (horse chestnut, *Aesculus hippocastanum*)**

While gastrointestinal obstruction would seem the most probable sequel, the bark, leaves and flowers of the horse chestnut tree are most toxic, causing vomiting, diarrhoea, hypersalivation abdominal tenderness, polydipsia and anorexia. Decontamination is generally not required.

**Daffodils (*Narcissus* species)**

The daffodil bulb contains the highest levels of calcium oxalate crystals, alkaloids and glycosides, which mainly induce vomiting and diarrhoea by direct irritation. The rest of the plant and even vase water can also cause mild signs. Decontamination would be justified when large amounts are known to have been ingested, and clinical signs can occur anywhere from 15 minutes to 24 hours after ingestion. Additional signs may include hyperthermia, hypotension, bradycardia, hyperglycaemia and rarely seizures.

**Overdoses of gastrointestinal medications**

Many owners take gastroprotectant medications, and hence overdoses of drugs such as omeprazole are common in veterinary medicine. It is extraordinarily unlikely for omeprazole overdose to cause significant clinical signs, and decontamination would not be recommended to that effect.

**Toxicants affecting the hepatobiliary system**

The liver has numerous roles including endocrine, exocrine, synthetic, metabolic and immunologic. In addition to these, the liver and biliary tree have central roles in toxicant metabolism and excretion respectively. As such, they are frequently exposed to potential damage in patients with intoxication, and even toxicants with no direct effect on these organs may result in biochemical abnormalities due to the patient’s systemic condition. While there is no consensus on the definitions of hepatic failure or injury in veterinary patients this article will use those previously described (Thawley 2017; Weingarten and Sande 2015) with acute liver failure (ALF) having acute onset of clinical signs, hyperbilirubinemia and prolonged prothrombin time (>1.5x the upper reference interval) with or without the presence of hepatic encephalopathy (HE). This means ALF is a functional failure of the liver, in contrast to acute liver injury (ALI) in which biochemical markers may indicate hepatic abnormalities while hepatic function (including glucose homeostasis, clotting protein synthesis and ammonia/urea handling) is preserved. In most cases, patients with ALI will recover fully with routine supportive treatment, and therefore this article will focus more on ALF. The ability to recognise life-threatening hepatobiliary dysfunction, pre-empt potentially fatal sequalae (such as HE, coagulopathy and sepsis), and alter dosing regimen of therapeutic agents are crucial to patient management.

**Mechanisms of hepatobiliary injury**

The liver is a major site of drug metabolism which can be broadly split into three phases. Firstly, modification of the drug occurs (including oxidation, reduction and hydrolysis by the cytochrome P450 enzyme system). Following modification drugs may be more or less physiologically active. If no water-soluble compound is generated from modification, then the drug undergoes conjugation (i.e. attachment of the compound to a polar molecule using glucuronidation, acetylation or sulphation) to form water soluble compounds before finally being excreted most commonly by either the biliary system or urine. Most drug metabolism occurs in zone 3 of the hepatic lobules which is also farthest from the hepatic blood supply and so can suffer dual injury of direct toxic metabolite induced damage and hypoxic damage (depending on the patient’s systemic state) (Chambers and others 2015). Drugs that cause hepatotoxicity may directly affect normal metabolic pathways, or they may mediate hepatic damage through free radical formation, toxicity to the mitochondrial pathways, hepatic immune cell activation (via stimulating the resident macrophages of the liver, also known as Kupffer cells) along with numerous other potential mechanisms of toxicity. Thankfully, a thorough understanding of the exact mechanism of each toxicant is not routinely helpful in the treatment of the patient. Table 2 lists some common toxicants, and any pertinent information (such as antidotes or important features).

**Table 2** – Selected common hepatotoxicants (Peterson and Talcott 2013; Berent 2015; Weingarten and Sande 2015; Thawley 2017)

|  |  |  |  |
| --- | --- | --- | --- |
| **Toxin** | **Mechanism** | **Other toxic effects** | **Notes** |
| **Plants** |
| Aflatoxins | Hepatic activation to reactive metabolite that damages DNA and proteins. Dose-dependent toxicity | May also cause renal proximal tubular necrosis. Granular urine casts indicative a poorer prognosis | May not exhibit elevated ALT. Often obtained from mouldy bread or grain. Chronic toxicity may cause immunodeficiency and hepatic neoplasia |
| Blue green algae (Microcystis aeruginosa) | Hepatocyte cytoskeleton disruption causing hepatic necrosis | Some other blue green algal species produce potent neurotoxins | May not exhibit elevated ALT. Severe signs may develop within hours of exposure |
| Mushrooms (most toxic are those containing amanitin) eg. Amanita phalloides (deathcap mushrooms) | Amanitin inhibits RNA polymerase and may also promote apoptosis | Affects rapidly dividing cells and therefore may also cause severe GI dysfunction and acute renal tubular necrosis | Mycologist may be needed to aid identification. Several phases to disease progression which may include false recovery prior to ALF |
| Sago palm (cycads) | Cycasin may cause ALF within 48-72hrs of ingestion | May cause non-specific signs (often GI dysfunction) within 24 hours of ingestion | Cycasin present in all parts of the plant but highest concentration within seeds |
| **Therapeutic agents** |
| Diazepam (oral) - cats | Idiosyncratic hepatic necrosis. Reported with repeated dosing | None significant | Toxicity seen 4-13 days after ingestion, also occurs with oral zolazepam |
| Lomustine (CCNU) | Idiosyncratic and dose-dependent reactions can be seen. ALI is common (up to 86% of patients), ALF uncommon | May also cause GI signs, altered haematologic findings and renal toxicity | Hepatic signs may progress to cirrhosis. Prophylactic S-adenosyl-L-methionine treatment may be protective against ALI |
| Methimazole - cats | Idiosyncratic hepatotoxicity, may have immune mediated component | None significant | None significant |
| NSAIDs (e.g. carprofen, ibuprofen) | Various mechanisms of toxicity including idiosyncratic reactions, mitochondrial toxicity and immune mediated reactions | May also cause GI signs (including bleeding), nephrotoxicity and neurotoxicity | Toxicity of other organ systems is more common than hepatotoxicity |
| Paracetamol (acetaminophen) | Hepatotoxic metabolites cause oxidative hepatic and red blood cell damage, and deplete glutathione stores | May cause methaemoglobinaemia | ALI often develops within 24-36 hours of exposure. N-acetylcysteine used as antidote |
| Phenobarbital | Poorly characterised. Hepatic enzyme induction occurs there is also dose-dependent toxicity, even animals on low doses can exhibit hepatic injury | May affect drug concentrations of many molecules metabolised by the P450 system. May reduce vitamin K dependent clotting factor activation in cats | Commonly causes elevated liver parameters not related to hepatotoxicity (frequently ALKP higher than ALT). May also lead to chronic hepatopathy/cirrhosis |
| Sulfonamides (e.g. TMPS) - dogs | Idiosyncratic hepatic necrosis | May cause several immune mediated syndromes | None significant |
| Xylitol - dogs | Causes hypoglycaemia (insulin release) and either dose dependant ALI /ALF or idiosyncratic ALF | May also experience marked electrolyte abnormalities (hypokalaemia, hypophosphataemia) | Hypoglycaemia can occur from ALF or massive hyperinsulinaemia |

**History, physical examination and laboratory evaluation**

Patients with hepatoxicity often have a short history of non-specific clinical signs such as gastrointestinal signs (vomiting, diarrhoea or evidence of gastrointestinal haemorrhage), lethargy, anorexia and abdominal pain or they may have more overt evidence of hepatic dysfunction such as icterus and altered mentation. Known access to hepatotoxins may be present but its absence cannot exclude intoxication.

Clinical signs will vary depending on the degree of hepatic dysfunction and any comorbid conditions, but the cardiovascular, respiratory and neurological systems should be prioritised initially. Neurologic impairment should be interpreted in light of the cardiovascular system; obtundation or stupor are not explicable by cardiovascular dysfunction unless there is a severe bradyarrhythmia, tachyarrhythmia, hypertension or hypotension. The presence of jaundice, melena and adequacy of the gag reflex should be carefully assessed in patients with severe hepatic dysfunction.

Routine haematology and biochemistry analyses are invaluable in the initial investigation of patients with hepatobiliary signs although the results vary widely depending on the severity of, and time elapsed since, intoxication. White blood cells may be elevated (due to non-specific inflammation, stress or infection), normal or decreased (due to overwhelming demand during sepsis, or with intoxications that also affect the bone marrow). Similarly, anaemia may be seen if coagulopathy or gastrointestinal bleeding has occurred, or if intoxication led to haemolysis. Thrombocytopenia may be seen due to consumption and endothelial sequestration (i.e. from haemorrhage and inflammation) but may also be exacerbated by reduced hepatic thrombopoetin production. Biochemical abnormalities are common even in mild intoxication. While parameters such as ALT and ALKP activity are often increased (and sometimes markedly so), markers of hepatic function such as bilirubin, glucose, urea, albumin, cholesterol and ammonia levels should be carefully evaluated, and serially monitored if there is concern for ALF. The contribution of other factors to these values may make assessment challenging, such as hypoglycaemia from sepsis or hyperbilirubinemia (which occurs with sepsis, haemolysis or hepatic swelling and intrahepatic biliary obstruction). Clotting times should be monitored, but prolonged values are not considered clinically significant until they exceed 30% of the upper reference range. In the absence of clinical bleeding or any requirement for an invasive procedure, prolonged clotting times alone do not justify plasma transfusion. If all clinicopathologic values are normal early in the course of intoxication, repeat assessment should be guided by the patient’s clinical progression.

**Differential diagnoses**

Although intoxication is an important differential diagnosis for patients with ALI/ALF, other differentials include leptospirosis, anaphylaxis (which in dogs frequently causes dramatic increases in ALT), hepatic lymphoma, hepatic lipidosis, portosystemic shunt, canine adenovirus-1, feline infectious peritonitis, salmonellosis and toxoplasmosis (Berent 2015). Depending on the patient’s stability, clinicopathologic derangements and clinical suspicion, hepatic fine needle aspirate can be useful for diagnosis/exclusion of hepatic lymphoma and lipidosis.

**Supportive care**

Where possible, any inciting toxicant should be withdrawn. Gastrointestinal decontamination (with/without activated charcoal depending on the toxicant) may be beneficial with recent exposures; induction of emesis should not be performed if the patient has a reduced level of consciousness or absent gag, and instead gastric lavage may be more appropriate if decontamination is considered vital. For lipid soluble toxins, intravenous lipid emulsion can be considered. In addition to specific considerations (outlined later in the article), general supportive care includes ensuring adequate perfusion and circulating blood volume using intravenous fluid therapy or blood products (for anaemic or coagulopathic patients) as indicated. The most appropriate fluid choice is somewhat controversial, as lactate containing fluids (such as Hartmann’s) may not be appropriately metabolised in patients with ALF, however what effect this actually has on the patient is unknown. Sodium chloride 0.9% is often advocated due to its acidifying effects, as alkalosis can worsen HE and should be avoided; however, fluid choice is typically determined based on the patient’s acid-base and electrolyte status, with frequent re-assessment during therapy. For patients with ALI, any balanced isotonic crystalloid fluid would be suitable as they should retain good hepatic function. Patients with refractory hypotension following volume restoration may require vasopressors.

Patients frequently exhibit vomiting and/or regurgitation, and antiemetics are commonly used. Gastroprotectant medication is often used where patients are considered high risk for gastrointestinal ulceration, although there is no evidence that it reduces the risk of gastrointestinal bleeding. Hepatoprotectant medication is recommended (although many require a patient able to tolerate oral medications), and S-adenosyl-L-methionine has been shown to be protective when administered before some hepatotoxins (such as lomustine); These drugs act by reducing hepatic oxidative stress, stabilising hepatocyte cell membrane structure and providing substrates (such as glutathione which is also an anti-oxidant) that enable ongoing hepatic metabolism.

Analgesia should be provided if patients have any source of discomfort, but caution is needed as many analgesics are metabolised by the liver. Given the risk of gastrointestinal ulceration NSAIDs are contraindicated therefore opioids are often used. It is best to use the lowest dose (such as 0.05mg/kg IV for methadone) and re-evaluate pain every 15-30 minutes, slowly titrating up to a suitable clinical response, as some patients with occult hepatic dysfunction may become acutely encephalopathic with higher or more frequent dosing.

Nutrition is an often-overlooked aspect of patient care. While many animals with ALI will have a short duration of illness, any patient who has poor caloric intake for 72 hours should be considered for assisted feeding, ideally enterally if this can be tolerated. Animals with ALF should have more aggressive nutritional intervention, as enteral nutrition may help maintain the health of the gastrointestinal tract, potentially reducing the risk of bacterial translocation. Naso-oesophageal or nasogastric tube placement is cheap and does not require a general anaesthestic, and diets with milk or vegetable protein are preferable to animal protein (due to their reduced risk of causing HE). The decision to place enteral feeding tubes must be carefully weighed against the risks in patients with coagulopathy.

For severely affected patients who are recumbent and/or have altered mentation, several important aspects of nursing care (such as ocular lubrication, turning and physiotherapy) are highlighted further in Table 4. Commonly used therapeutic agents and their doses are given in Table 3.

**Table 3** – Commonly used therapeutic agents

|  |  |  |  |
| --- | --- | --- | --- |
| Class | Drug | Route | Dose |
| Gastroprotectants  | Omeprazole | IV/PO | 1mg/kg q12 hr |
| Anti-emetics | Maropitant | IV/SC | 1mg/kg q24 hr |
| Pro-kinetics | Metoclopramide | IV | 1-2mg/kg/day (CRI) |
| Antimicrobials (only if required for leptospirosis or sepsis) | Amoxiclav | IV | 20mg/kg q8 hr |
| Hepatoprotectants | S-adenosyl-L-methionine  | PO | 20mg/kg q24 hr |
| Ursodeoxycholic acid | PO | 10-15mg/kg q24 hr |
| Vitamin E | PO | 15IU/kg q 24 hr |
| N-acetylcysteine | IV | 140mg/kg once, then 70mg/kg every 6 hr for 72 hrs\* |
| Silymarin | PO | 8-20mg/kg q8 hr |
| Analgesics | Methadone | IV | 0.05mg/kg titrated upwards (total 0.4mg/kg q4 hr) |

CRI – Continuous rate infusion

\* Care with the volume infused in cats

N.B. As many of these medications are not licenced, appropriate owner consent should be obtained with discussion of any risks

As patients with ALI seldom develop HE or coagulopathy, supportive treatment may be all that is required for a successful outcome. In cases with ALF, more serious consequences can occur and are discussed below. It should also be noted that patients with ALF may have difficulty metabolising medication, and while the appropriate dose reduction is not known, the BSAVA Small Animal Formulary Appendix (Ramsey 2017) lists drugs that may require dose adjustments.

**Specific considerations for patients with acute liver failure**

**Hepatic encephalopathy**

Hepatic encephalopathy may be difficult to distinguish from decreased responsiveness due to pain, discomfort or distress, or decreased CNS perfusion seen in systemically unwell patients, or those with neurologic manifestations of intoxication. While most consider HE to cause coma, it is important to remember that it can also cause hyperexcitability, and some patients will shift between the two states. As mentioned earlier, it is vital that emesis is not induced in patients who are considered neurologically abnormal or who have a questionable gag reflex. The pathogenesis of HE is complex and multifactorial, ammonia is only one aspect of its development (Lidbury and others 2016). Sequelae can include elevated intracranial pressure, and the most useful clinical marker of this is the level of mentation. Animals at risk of HE may benefit from serial Modified Glasgow Coma Scale (Shores 1983) scoring to document acute changes in their level of mentation. The Cushing’s reflex is considered to be a very late stage event in patients with elevated intracranial pressure, and in the authors’ experience is also inconsistent so should not be relied upon; in cardiovascularly stable patients with biochemical changes consistent with ALI/ALF and altered mentation, HE and increased intracranial pressure should be suspected and treated for (as outlined in Table 4) unless there is a contraindication (Berent 2015; Lidbury and others 2016).

**Table 4** – Treatment of patients with hepatic encephalopathy

|  |  |  |
| --- | --- | --- |
| Rationale | Intervention | Notes |
| Reduce ICP | Elevate head (15-30 degrees) | Do not use a towel under the neck to elevate the head as this can compress the jugular veins – instead place the cranial half of the body on a rigid board and elevate this |
| Avoid compression of neck or eyes |
| Hyperosmolar therapy (Mannitol 0.5-1g/kg IV through filter over 20 mins OR 3-5ml/kg IV hypertonic saline (7.2-7.5%) over 20 mins | Care in patients with hypervolaemia, sodium derangements or oligoanuric renal disease |
| Maintain cerebral oxygen delivery | Supplemental oxygen | Do not use nasal prongs/cannulae if they cause patient sneezing or coughing as this increases ICP |
| Treat hypotension with fluid therapy to maintain cerebral perfusion | Normalise blood pressure |
| Reduce blood ammonia concentrations | Lactulose Oral: Wide dose range, titrate to a soft stool consistencyRetention enema: 10-20ml/kg total volume, 3 parts lactulose to 7 parts warm water | Lactulose binds ammonia within the GI tract, alters GI flora to less ammoniagenic organisms and enhances voiding of GI content |
| Avoid alkalaemia and hypokalaemia | These cause renal ammonia production |
| Reduce cerebral metabolic rate | Aggressively treat seizure activity | Levetiracetam 60mg/kg IV loading dose followed by 20mg/kg IV q8 hr (this can also be given using a retention enema)Phenobarbital is the second choice due to its potential hepatic side effects |
| Avoid pyrexia/hyperthermia |  |
| Avoid further complications | Serial monitoring of gag reflex to reduce aspiration risk | If gag is questionable or absent, intubate with a cuffed ET tube immediately |
| Frequent turning and physiotherapy | To decrease the risk of dermatitis, ulceration and discomfort |
| Ocular lubrication | Exposure keratitis and corneal ulceration is common |
| Faecal and urinary care |  |
| Reduce exacerbating factors | Sepsis, GI bleeding, electrolyte and acid base changes |  |

**Haemorrhage**

Coagulation and fibrinolysis are complex and well-balanced systems. Although severe liver disease is a well-known risk factor for spontaneous haemorrhage, it may be better to think of such patients as having an altered equilibrium to their coagulation system as hepatic dysfunction can actually be pro-coagulant as well. Spontaneous haemorrhage in patients with ALF is uncommon, but when it occurs the results are frequently catastrophic. Patients with ALF have many reasons to develop haemorrhage, including gastrointestinal ulceration directly due to the ALF and portal hypertension, reduced coagulation factors (from both hepatic dysfunction and consumption), disseminated intravascular coagulation (which may be exacerbated by sepsis) and the potential for an acquired vitamin K deficiency (cholestasis impairs absorption of vitamin K as it is fat soluble). While one must be cognisant of these possibilities, a more difficult question is how to treat these patients. In patients that are actively bleeding or requiring invasive procedures (surgery or hepatic biopsy), plasma transfusion is indicated as it restores all clotting factors. The treatment of choice is fresh frozen plasma as it replaces multiple clotting factors, and a dose of 10-20ml/kg is often cited as an initial target, with serial re-assessment based on clinical response. Vitamin K1 may also be empirically administered at 0.5-1mg/kg SC/IV q12-24hrs. When prolonged coagulation times are appreciated without bleeding, there is no indication for plasma therapy and it may be harmful as transfusion reactions are not infrequent (Softley and others 2015).

**Hypoglycaemia**

The liver is an important regulator of glucose homeostasis as it both stores excess carbohydrate (as glycogen) and generates glucose from other molecules by gluconeogenesis. Hypoglycaemia during intoxication has several possible causes, including hepatic dysfunction, toxicants directly affecting blood glucose concentration (e.g. xylitol) and sepsis. Regardless of cause, the best course of action is to administer a bolus doe of glucose if the hypoglycaemia is marked and supplement the patient’s intravenous fluids with glucose (using a 2.5-5% solution).

**Aspiration pneumonia**

Patients with hepatotoxicity commonly experience vomiting and regurgitation. Those who experience severe hepatic dysfunction may exhibit reduced level of consciousness or be recumbent for prolonged periods, both of which increases the risk of aspiration pneumonia.

**Sepsis**

Although toxicants do not directly cause sepsis, those severely affecting the liver can predispose to its development. Complement is an important part of the immune response, and in patients with severely compromised hepatic function, the resultant lack of complement weakens the immune system response to infection. Hepatic failure can cause increased portal venous pressure, which in turn may cause dysfunction or ulceration of the gastrointestinal tract leading to a higher chance of bacteria translocating into the portal vasculature and being transported to the liver. Routine hepatic clearance of these organisms by the resident Kupffer cells may also be impaired during hepatic injury. Together, these factors contribute to the increased risk of sepsis in patients with liver failure and in people common sites of sepsis with acute liver failure include the bloodstream, urogenital and respiratory tracts and indwelling devices (such as intravenous catheters). In people it is recommended to provide broad spectrum antimicrobials to any patient with hepatic failure and concurrent systemic inflammation, worsening HE, or vasopressor refractory hypotension.

**Prognosis**

For patients with ALI the prognosis is normally very good. In the authors’ experience patients with ALF and HE require aggressive support for a successful outcome, and if sepsis or spontaneous haemorrhage occurs the prognosis becomes significantly more guarded. One study (not limited to toxicant related ALF alone) reported survival of only 14% and should the owners be able to, referral for specialist care is recommended for ALF.

**Questions**

1. Which of the following is the best marker of elevated intracranial pressure?
2. Pupil size and reactivity
3. Worsening level of mentation – CORRECT ANSWER
4. Serum ammonia concentration
5. Absence of the Cushing reflex
6. In patients with poor mentation and possible hepatotoxicity which of the following should be done?
7. Assess the cardiovascular system and treat hypotension if found
8. Assess gag reflex and intubate if absent
9. Consider the presence of hepatic encephalopathy
10. All of the above – CORRECT ANSWER
11. **Which of the following drugs does not have any prokinetic activity?**
12. Ondansetron – CORRECT ANSWER
13. Metoclopramide
14. Cisapride
15. Erythromycin
16. **Acute kidney injury is known to occur in ibuprofen intoxication at or above what dose?**
17. 10mg/kg
18. 50mg/kg
19. 100mg/kg
20. 175mg/kg – CORRECT ANSWER

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