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Presents...

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Acetaminophen (Paracetamol) and NSAID Toxicity

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Acetaminophen and NSAID Toxicities
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Acetaminophen

Acetaminophen (Paracetamol, non-aspirin pain reliever, APAP) is a synthetic, non-opiate, derivative of p-aminophenol. Acetaminophen’s exact mechanism of action is unknown but it is believed to block the production of prostaglandins from arachidonic acid by inhibiting COX-3. Acetaminophen acts primarily in the CNS to increase the pain threshold, and it may also inhibit chemical mediators that sensitize the pain receptors to mechanical or chemical stimulation. The antipyretic activity of acetaminophen is achieved by blocking the effects of endogenous pyrogens by inhibiting prostaglandin synthesis.

Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma levels are seen at 10-60 minutes for regular products, and at 60-120 minutes for extended release forms. Two major pathways are used to metabolize acetaminophen by most species (P-450 metabolism followed by conjugation via glucuronidation or sulfation).

Acetaminophen-induced hepatotoxicity and nephrotoxicity is due to the formation of the metabolite, N-acetyl-para-benzoquinoneimine (NAPQI), in the liver and to a lesser degree in the kidney. NAPQI binds covalently to sulphhydryl groups on tissue macromolecules leading to cell necrosis. Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to the hepatic cell membrane and damages the lipid layer. Large doses of APAP can cause nephrotoxicity characterized by proximal tubule necrosis. Another metabolite, para-aminophenol (PAP), has been show to damage the RBCs, leading to methemoglobinemia and Heinz body formation.

Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs seen with acetaminophen toxicity include depression, weakness, hyperventilation, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, death, cyanosis, dyspnea, and hepatic necrosis. Other possible clinical signs include metabolic acidosis, renal insufficiency/damage, myocardial damage, coma, thrombocytopenia, and vomiting. Liver necrosis is less common with cats than with dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks. Hepatotoxicity has been reported in dogs at doses of 100 mg/kg, and 200 mg/kg caused clinical methemoglobinemia in 3 out of 4 dogs. Doses of 40 mg/kg have resulted in Keratoconjunctivitis Sicca (KCS) 72 hours after ingestion. Cats developed clinical signs at doses > 40 mg/kg.
in one study, however no dose is safe in cats since they are deficient in glucuronyl transferase. Ferrets are considered to be as sensitive as cats.

Early decontamination is most beneficial. Emesis can be performed in the asymptomatic animal, unless contraindicated. Activated charcoal adsorbs acetaminophen and may need to be repeated, due to entero-hepatic recirculation. A cathartic should also be used, unless the animal is dehydrated or has diarrhea. Monitor liver values, and for the presence of methemoglobinemia. ALT, AST and bilirubin may rise within 24 hours after ingestion and peak within 48 to 72 hours. Serum albumin concentrations decrease significantly after 36 hours and continue to decrease during liver failure, providing a true index of liver function.

Symptomatic patients need initial stabilization, including oxygen if dyspnoeic. Treatment involves replenishing the glutathione stores and converting methemoglobin back to hemoglobin. N-acetylcysteine (Mucomyst®, NAC) is hydrolyzed to cysteine and becomes a precursor in the synthesis of glutathione, or can also be oxidized to the organic sulfate needed for the sulfation pathway. This provides sulfhydryl groups which bind with acetaminophen metabolites to enhance elimination.

NAC is available in 10% and 20% solutions. An initial oral loading dose for NAC is 140 mg/kg of a 5% concentration (can be diluted in 5% Dextrose or sterile water). This is followed with 70 mg/kg PO QID for generally 7 treatments. With ingestion of massive quantities some authors suggest using 280 mg/kg for a loading dose and continuing treatment for 12 to 17 doses. Adverse effects of the oral route of NAC include nausea and vomiting. Not all NAC is labeled for IV use, however the loading dose (diluted to 5%) could be given slow IV over a period of 15 to 20 minutes with use of a bacteriostatic filter (0.2 micron), in life-threatening cases. A two-to-three hour wait between activated charcoal administration and PO administration of NAC is recommended, since activated charcoal could adsorb NAC as well as acetaminophen. Fluid therapy is used to correct dehydration and for maintenance needs, not for diuresis. Whole blood transfusions or oxyglobin may be necessary to increase oxygen carrying capacity.

For hepatic injury, a new therapy that shows potential is s-adenosylmethionine (SAMe, Denosyl-SD4®) at 20 mg/kg/day. Early studies and anecdotal reports show a positive effect for treatment of acetaminophen toxicosis. OTC formulations of SAMe have variable potency; so use a prescription quality, enteric coated product (round the dose to nearest whole pill and do not break pill). Steroids and antihistamines are contraindicated.
Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have poor to guarded prognosis. Treatment may continue for weeks.
Ibuprofen

Ibuprofen (Nurofen, Brufen, etc.) is a nonsteroidal anti-inflammatory agent (NSAID). Ibuprofen inhibits prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Ibuprofen decreases secretion of the protective mucous layer in the stomach and small intestine and causes vasoconstriction in gastric mucosa. Ibuprofen inhibits renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. Ibuprofen may also affect platelet aggregation and possibly hepatic function. Serious hepatotoxicosis does not appear to be a common problem with ibuprofen.

Absorption of ibuprofen is rapid (0.1 to 1.5 h). Plasma half-life in the dog has been reported to be 2-2.5 hours, but the elimination half-life is considerably longer. Ibuprofen is metabolized in the liver (conjugation, oxidation and hydroxylation) and undergoes significant entero-hepatic recirculation before being excreted in the urine. Fifty to sixty percent is excreted in the urine as metabolites within 24 hours, with less than 10% excreted in the urine unchanged. The remainder of the drug is eliminated in feces, both as metabolites and as unchanged drug. Geriatric animals and neonates are at higher risk of toxicosis as acute renal insufficiency, liver disease, and hypoalbuminemic states can decrease plasma protein binding, decrease metabolism and increase volume of distribution. Administration of ibuprofen in combination with glucocorticoids, salicylates, phenylbutazone, indomethacin, or other NSAIDS could potentiate the adverse effects of these drugs.

Ibuprofen has a narrow margin of safety. Even at the therapeutic dog dosage of 5 mg/kg, ibuprofen may cause gastric ulcers and perforations with chronic use. In dogs, an acute exposure of 50-125 mg/kg can result in gastrointestinal signs (vomiting, diarrhea, nausea, abdominal pain, anorexia), > 175 mg/kg can result in more severe GI signs (hematemesis, melena) plus renal damage (pu/pd, oliguria, uremia). Doses of > 400 mg/kg in the dog result in GI and renal signs, plus CNS signs (seizure, ataxia, coma, shock). Cats are thought to be twice as sensitive to ibuprofen’s toxic effects as dogs due to their limited glucuronyl-conjugating capacity. Ferrets that ingest ibuprofen are at high risk for CNS depression and coma, with or without GI upset.

The onset of GI upset is generally within the first 2-6 hours after ingestion, with the onset of GI hemorrhage and ulceration occurring 12 hours to 4 days post ingestion. Lesions associated with ibuprofen overdose include perforations, erosions, ulcers, and hemorrhages in the upper (stomach and duodenum) and, on occasion, lower (colon) gastrointestinal tract. The onset of renal failure often occurs within the first 12 hours after massive exposure to an NSAID but may be delayed until 3-5 days after exposure.
Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs ibuprofen and may need to be repeated, since ibuprofen undergoes entero-hepatic recirculation. A cathartic should also be used, unless the animal is dehydrated or has diarrhea. In the asymptomatic patient, gastric protection should be continued for 5-7 days. Animals should be started on IV fluids at twice maintenance for 48 hours if renal failure is expected. Monitor BUN, creatinine, and urine specific gravity (baseline level, 24, 48, and 72 h). The animal may also need to be monitored for acidosis and electrolyte changes. Acid-base disturbances are rare and usually transient. Peritoneal dialysis may be necessary if unresponsive oliguric or anuric renal failure develops.

For symptomatic animals, Gl protectants are very important. Mild gastrointestinal irritation may be treated symptomatically with antacids, such as magnesium or aluminum hydroxide. Misoprostol is helpful for treating or preventing gastric ulceration caused by NSAIDS as it stimulates mucus and bicarbonate secretion and increases gastric mucosal blood flow (contraindicated during pregnancy due to its abortifacient activity). H2 blockers, sucralfate and omeprazole can also be used to manage and/or prevent gastric ulcers. Assisted ventilation and supplemental oxygen may be required if animal is comatose. Seizures should be treated with diazepam. Fluids, whole blood, inotropic agents, and electrolytes should be given to control hypotension and hemorrhage, maintain renal function, and correct electrolyte abnormalities.

Prognosis is good if the animal is treated promptly and appropriately. Gastrointestinal ulceration usually responds to therapy. Acute renal insufficiency resulting from ibuprofen administration has been considered reversible, however, the development of papillary necrosis is generally considered irreversible.
Carprofen (Rimadyl®) is a nonsteroidal anti-inflammatory agent (NSAID). NSAIDs inhibit prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. They decrease secretion of the protective mucous layer in the stomach and small intestine and cause vasoconstriction in gastric mucosa. NSAIDs inhibit renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. Idiosyncratic hepatotoxicosis can occur with exposure to carprofen.

The therapeutic dose of carprofen in dogs is 4.4 mg/kg PO SID or 2.2 mg/kg PO BID. In dogs, an acute exposure of 20 - 50 mg/kg can result in gastrointestinal signs (vomiting, diarrhea, nausea, abdominal pain, anorexia) and doses > 50 mg/kg can result in more severe GI signs (hematemesis, melena) plus renal damage (pu/pd, oliguria, uremia). Cats are more sensitive to carprofen’s toxic effects than dogs due to their limited glucuronyl-conjugating capacity. Doses > 4 mg/kg in cats can cause GI effects and renal effects are possible at doses > 8 mg/kg in cats. Following overdosage, elevations in ALT and Alkaline Phosphatase are also possible and may require treatment.

Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs carprofen and may need to be repeated, since carprofen undergoes entero-hepatic recirculation. A cathartic should also be used, unless the animal is dehydrated or has diarrhea. In the asymptomatic patient, gastric protection should be continued for 5-7 days. Animals should be started on IV fluids at twice maintenance for 48 hours if renal failure is expected. Monitor BUN, creatinine, and urine specific gravity (baseline level, 24, 48, and 72 h). The animal may also need to be monitored for acidosis and electrolyte changes. Acid-base disturbances are rare and usually transient. Peritoneal dialysis may be necessary if unresponsive oliguric or anuric renal failure develops.

For symptomatic animals, GI protectants are very important. Mild gastrointestinal irritation may be treated symptomatically with antacids, such as magnesium or aluminum hydroxide. Misoprostol is helpful for treating or preventing gastric ulceration caused by NSAIDS as it stimulates mucus and bicarbonate secretion and increases gastric mucosal blood flow (contraindicated during pregnancy due to its abortifacient activity). H2 blockers, sucralfate and omeprazole can also be used to manage and/or prevent gastric ulcers. Fluids, whole blood, inotropic agents, and electrolytes should be given to control hypotension and hemorrhage, maintain renal function, and correct electrolyte abnormalities.
Prognosis is good if the animal is treated promptly and appropriately. Gastrointestinal ulceration usually responds to therapy. Acute renal insufficiency resulting from carprofen administration has been considered reversible, however, the development of papillary necrosis is generally considered irreversible.