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Paracetamol (also known as acetaminophen or APAP in some countries) is a very widely and readily available non-narcotic analgesic. It is not used therapeutically in cats.

Paracetamol is sold under many brand names and is available in many formulations including tablets, capsules, liquid suspensions and powder preparations (usually for mixing with water). Tablets are typically 500 mg (or 250 mg for children over 6 years of age) and suspensions 120 mg/5 ml or 250 mg/5 ml. Paracetamol is also commonly available in compound products with other drugs including codeine, caffeine, aspirin, ibuprofen and decongestants.

**Exposure**

Cats may be exposed after eating a paracetamol-containing product but poisoning can also occur when an owner, believing their cat to be unwell, misguided gives them part or a whole tablet or doses them with a few millilitres of a paediatric paracetamol suspension.

The Veterinary Poisons Information Service (VPIS) is a 24-h telephone emergency service providing information on the management of actual and suspected poisoning in animals. It provides direct support to veterinary professionals worldwide.

See http://vpisglobal.com/ for more information and how to sign your practice up to receive this vital service.
**Mechanisms of toxicity**

**Cats are different**

Cats are very sensitive to paracetamol. In particular they may develop methaemoglobinaemia (high blood levels of methaemoglobin; an oxidised form of haemoglobin which cannot bind oxygen), haemolytic anaemia, Heinz body formation and hepatic necrosis.

In all species paracetamol is metabolised in the liver by glucuronidation, sulphation and oxidation (Figure 1). The glucuronide and sulphate conjugates are non-toxic and are excreted in bile and urine. In most species the oxidation pathway is minor whilst glucuronidation is the major pathway of paracetamol metabolism. Cats, however, have a restricted ability to conjugate with glucuronic acid as they have low levels of glucuronyl transferase, the enzyme that catalyses the final step of the glucuronidation pathway. They, therefore, have a limited ability to metabolise paracetamol to non-toxic metabolites.

**The toxic metabolite**

The oxidation pathway produces a highly reactive compound called N-acetyl-p-benzoquinoneimine (NAPQI). Normally this compound is conjugated with glutathione, then further metabolised to non-toxic metabolites. At low dosing this is an effective and efficient detoxification pathway despite the fact that cats have low glutathione concentrations. At higher paracetamol doses, the glucuronidation and sulphation routes are saturated and the oxidation pathway increases in activity. This results in increased production of NAPQI, causing glutathione depletion in the liver. NAPQI then binds with cellular molecules and proteins causing cell death in the liver.

**Oxidising metabolites**

Alternative metabolic pathways also allow accumulation of oxidising metabolites that may

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**Figure 1:** Paracetamol in cats — proposed metabolism and mechanism of toxicity. *N-acetylation of compounds involves two enzymes, N-acetyltransferase 1 and N-acetyltransferase 2 (NAT1 and NAT2). Cats have only NAT1 and dogs have no NAT enzymes.
induce methaemoglobin formation, Heinz body formation and denaturation of erythrocyte membranes. In the presence of glutathione, methaemoglobin will be reduced to haemoglobin. However, as glutathione becomes depleted insufficient quantities will be available for this reduction reaction. Methaemoglobin concentrations in blood rise (it is typically measured as a percentage of haemoglobin) and tissue hypoxia occurs. Heinz bodies are denatured chains of haemoglobin with oxidised sulphydryl groups. They precipitate and migrate towards cell membranes where they render cells fragile. Haemolysis and restricted passage of erythrocytes through the microcirculation and spleen may result in anaemia.

It has been suggested that the metabolite para-aminophenol, and not NAPQI, is responsible for the methaemoglobinaemia seen in cats and dogs with paracetamol poisoning.1 This is a minor metabolite of paracetamol that is removed as N-acetyl conjugates. Cats have only one of the enzymes responsible for this reaction and dogs have none. This means that both species are less efficient at removing this toxic metabolite which is known to undergo reactions with oxyhaemoglobin. Humans, who frequently overdose with paracetamol and possess both enzymes, do not develop methaemoglobinemia due to paracetamol toxicity.

**How the antidotes work**

**Acetylcysteine (previously N-acetylcysteine, NAC)**
The most widely used antidote in paracetamol poisoning is acetylcysteine because it can reduce the toxicity of the drug by three main mechanisms:

- Acetylcysteine is a precursor of glutathione and is metabolised to form a substrate for glutathione synthesis in red blood cells and the liver.
- Acetylcysteine acts directly on the reactive metabolite NAPQI to form an acetylcysteine conjugate which can be excreted (although this reaction is slow).
- Acetylcysteine is oxidised in the liver to form sulphate thereby increasing the capacity of the sulphation pathway.

Administration of acetylcysteine has been shown to reduce the half-life of paracetamol by half in cats.2

**S-adenosyl-methionine (SAMe)**
S-adenosyl-methionine (SAMe) is also a precursor of glutathione, reducing methaemoglobin to haemoglobin. In mice, SAMe significantly reduced paracetamol toxicity and was more potent than acetylcysteine in reducing liver toxicity.3 Administration 1 h after paracetamol ingestion provides protection by reducing oxidation and Heinz body formation, but treatment after 4 h in cats may be of limited benefit.4

**Ascorbic acid**
Ascorbic acid can be given to reduce methaemoglobin to haemoglobin, although the reaction occurs slowly.5 There is some evidence to suggest it may also...
Toxic dose

The toxic dose of paracetamol in cats is 50–00 mg/kg. In an experimental study cats given 90 mg/kg showed a rapid increase in methaemoglobin formation within 4 h of ingestion. One cat died at 24 h without treatment. A second cat that had been treated with SAMe 1 h after dosing was found in distress at 36 h, failed to respond to supportive care and was euthanased. In another study a dose of 60 mg/kg in cats produced a methaemoglobinaemia of 22% in 4 h whereas a dose of 120 mg/kg produced a concentration of 45%. In essence, one tablet of paracetamol is likely to cause severe toxicity in a cat (Figure 2).

Time course

Paracetamol is rapidly absorbed from the gastrointestinal tract under normal conditions and clinical manifestations of paracetamol ingestion may occur within 4 h in cats, but definitely within 6–24 h. Recovery in treated cats usually occurs within 2 days, depending on the severity of signs, but biochemical abnormalities may take
several weeks to return to normal concentrations.\textsuperscript{15}

**Clinical signs**

**Early effects (typically 1–4 h)**

Progressive cyanosis is the most striking sign in cats with paracetamol toxicity and is associated with tachycardia, tachypnoea and dyspnoea. Mucous membranes appear brown in colour, and weakness and lethargy may be observed.

**Tip**

Clinical signs of paracetamol toxicity include cyanosis with tachypnoea and dyspnoea, facial and paw oedema, depression, vomiting and haematuria. If a cat presents with consistent clinical signs the owner should be questioned about exposure to paracetamol.

**At 4–24 h**

Facial and paw oedema may be observed in some cases. Depression, vomiting, anorexia and vocalisation may occur and dark brown blood may be noted indicating the presence of methaemoglobinemia.\textsuperscript{9} Haematuria, anaemia, and evidence of haemolysis may be present. Less common effects include hyper- or hypothermia, ataxia and lethargy.

**Later effects (day 2–7)**

Although raised liver enzymes and bilirubin have been reported in cats,\textsuperscript{12} hepatic necrosis is not the principal cause of fatality in cats as they usually die as a result of severe methaemoglobinemia. Haemoglobinuria, intravascular haemolysis, jaundice and other evidence of liver damage may be seen in animals that survive the initial stages of paracetamol poisoning. Coma, convulsions and pulmonary oedema are occasionally reported. Oliguria and renal damage can occur after high doses, although the exact dose is unknown in cats.\textsuperscript{14}

**Prognosis**

The prognosis of cats with paracetamol toxicity is good with prompt treatment but depends on the severity of methaemoglobinemia.\textsuperscript{9,13} It also appears that time between ingestion and treatment may be as important, or even more important, than the dose ingested.\textsuperscript{13} Coma, convulsions and pulmonary oedema are poor prognostic signs.

**Diagnosis**

Diagnosis of paracetamol is based on clinical signs and history. It is important to ask the owners if they have given their cat any medication. Laboratory changes may also aid diagnosis with changes in haematology, methaemoglobin concentration, liver enzymes and urinalysis (Box 1).

**Box 1: Diagnosis of paracetamol toxicity**

A diagnosis of paracetamol toxicity is made by:
- **clinical signs;**
- **history** — have the owners treated their cat with any medication?;
- **laboratory changes,** including:
  - Heinz body anaemia, decreased packed cell volume;
  - methaemoglobin >15\% (a drop of blood on paper towel will appear brown), usually begins within 4 h;\textsuperscript{7,10}
  - serum chemistry profile — increased liver enzyme activity from 24–36 h;\textsuperscript{14}
  - urinalysis (haemoglobinuria, proteinuria and bilirubinuria).
Treatment
Decontamination
The aim of treatment for a cat with paracetamol toxicity is to ensure adequate oxygenation and prevent further metabolism of paracetamol to toxic metabolites with the use of antidotes and to prevent damage to the liver and red blood cells. Any cat with signs consistent with paracetamol toxicity should be treated irrespective of the time since ingestion or the dose ingested. If ingestion was recent an emetic and activated charcoal can be considered, depending on the clinical condition of the cat.

Antidotal therapy
Antidotal therapy should be started in any cat with signs of toxicity or that has ingested a potentially toxic dose (Table 1). Acetylcysteine is the antidote of choice and if not available in the practice can usually be obtained from your local hospital emergency department (since it is used for humans with paracetamol poisoning). It can be given by intravenous infusion or orally; however, it has a sulphurous smell and taste which can cause significant hypersalivation so it needs to be diluted to improve palatability or given by naso-oesophageal tube if clinically indicated. SAMe and ascorbic acid can also be given in combination with acetylcysteine.

Monitoring and supportive care
Other treatment is essentially supportive with monitoring for signs of hypoxia, methaemoglobinaemia, liver damage, anaemia, haemolysis and renal impairment. Oxygen will be required in cats with cyanosis and in cats with severe respiratory signs oxyglobin (haemoglobin glutamer) can be given. Whole blood transfusions may be required in cats with evidence of severe haemolysis, significant decrease in packed cell volume (PCV) or severe anaemia.

Conclusions
Increased metabolism of paracetamol via the oxidative pathway with unopposed production of toxic metabolites causes toxicity in cats following paracetamol administration. The characteristic picture is one of methaemoglobinaemia, cyanosis, anaemia and jaundice. Death usually occurs from progressive methaemoglobinaemia or, more rarely, from severe hepatic necrosis. The aim of treatment for the cat with paracetamol toxicity is to ensure adequate oxygenation and

Table 1: Dosages of antidotes for the management of paracetamol poisoning

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<th>Drug</th>
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| Acetylcysteine | • **IV or oral:** 140 or 280 mg mg/kg diluted in 12–25 ml/kg of fluid IV over 6 h, followed immediately by 70 mg/kg IV (over 15–20 minutes) every 6 h for 36 h or more dependent on the clinical condition of the animal  
• Continue treatment until cat is clinically well  
• Can be diluted in dextrose or saline |
| SAMe       | • **Oral:** 90 mg twice daily for 3 days, then 90 mg daily for 14 days |
| Ascorbic acid | • **SC:** 30–40 mg/kg every 6 h for at least 36 h |
prevent further metabolism of paracetamol to toxic metabolites with the use of antidotes, particularly acetylcysteine, and to prevent damage to the liver and red blood cells.

References


3. Terneus MV, Brown JM, Carpenter AB, et al. Comparison of S-adenosyl-L-methionine (SAMe) and N-acetylcysteine (NAC) protective effects on hepatic damage when administered after acetaminophen overdose. Toxicology 2008; 244: 25–34.


7. Rumbeiha WK and Oehme FW. Methylene blue can be used to treat methemoglobinemia in cats without inducing Heinz body hemolytic anemia. Vet Hum Toxicol 1992; 34: 120–122.


