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Successful therapeutic management of Acetaminophen toxicity in a kitten

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Abstract
A five months old male kitten weighing about 1.3 kg was presented with the history of weakness, anorexia, vomiting and diarrhoea after administration of 250 mg acetaminophen tablet for fever. The kitten was in sternal recumbency and depressed mental state. Normal temperature (38.3º C), tachycardia (96/min), dyspnoea, brown colour mucous membrane and facial oedema (Fig 1) were observed. Haematobichemical examination revealed moderate anaemia and elevated blood urea nitrogen, creatinine, total billirubin, alanine aminotransferase and alkaline phosphatase. The kitten was treated with N-acetylcystine (NAC), ringers lactate, ascorbic acid, ranitidine and S-adenosyl methionine (SAMe). It showed uneventful recovery on fifth day.

Keywords: Cat, acetaminophen toxicity, paracetamol, N-acetylcystine

Introduction
Acetaminophen toxicity is the second most common cause of Non-steroidal anti-inflammatory drug toxicities in cats (Aronson and Drobatz, 1996) [3]. Acetaminophen is a synthetic non-opiate derivative of p-aminophenol and is popularly known as paracetamol which is one of the major over the counter medicine used in human beings for relieving pain and fever (Plumb, 1999) [10]. Acetaminophen is metabolized in the liver thorough glucuronidation and sulfation. When these pathways are saturated or deficient, acetaminophen is oxidized in alternate pathway and cause break down of acetaminophen into toxic metabolite, N–acetyl-p-benzoquinoneimine (NAPQI) by cytochrome P-450 enzyme. NAPQI is a free radical that damages haemoglobin, red blood cells, liver and kidney (Aronson and Drobatz, 1996; Richardson, 2000) [3, 12]. The drug is well tolerated by human beings but the cats are more sensitive due to deficiency of glucuronidation and sulfation. The toxic effect of NAPQI is limited by its conjugation with glutathione. Cats have low level of glucuronyl transferase which is responsible for final step in glucuronidation pathway and also have low level of glutathione concentration which is needed to conjugate with NAPQI to produce non-toxic metabolite, mercapturic acid and excreted through urine (Aronson and Drobatz, 1996; Perry, 1998) [3, 9]. Excess acetaminophen suppresses the glutathione synthesis (Court, 2001) [4]. It is available in different forms like tablets, suspensions, capsules, suppositories and injectables. The present paper describes the toxicity in a kitten with high dose of acetaminophen and its medical management.

Case history and observation
A five months old male kitten weighing about 1.3 kg was presented to small animal medicine unit, Veterinary Clinical Complex, Veterinary College and Research Institute, Namakkal with the history of weakness, anorexia, vomiting and diarrhoea. It was administered with 250 mg of acetaminophen tablet twelve hours back by the owner for fever. The kitten was in sternal recumbency and depressed mental state. Normal temperature (38.3º C), tachycardia (96/min), dyspnoea, brown colour mucous membrane and facial oedema (Fig 1) were observed. Haematobichemical examination revealed decreased haemoglobin, packed cell volume (PCV), total erythrocyte count (RBCs) and elevated blood urea nitrogen (BUN), creatinine, total billirubin, alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (Table 1).

Treatment and discussion
The kitten was treated with N-acetylcystine (NAC) (@140 mg/kg bwt po and followed by 70

mg/kg bwt po for every 6 hours once for seven times), ringers lactate (@ 10 ml/kg iv),ascorbic acid (@ 30 mg/kg iv), ranitidine (@ 0.5 mg/kg iv) and S-adenosyl methionine (SAMe) (@ 90 mg po) for five days. The kitten showed substantial reduction in facial oedema and able stand on second day. The animal started consuming milk on third day. It showed uneventful recovery on fifth day. The most common cause of acetaminophen toxicity in cats was due to accidental exposure and deliberate administration by the owner (Aroson and Drobatz, 1996; Pothiappan *et al*., 2014) [3, 11]. The clinical signs might occur within few hours of ingestion due to rapid absorption in gastrointestinal tract with single toxic dose or repeated dosages. There was no safe acetaminophen dose for cats. The toxic dose was reported as 50 to 100 mg/kg bwt but the clinical signs of acetaminophen toxicosis in cats occurred at dose as low as 10 mg/kg (Marcella, 1983; Osweiler, 1997; Richardson, 2000; Sellon, 2001) [6, 8, 12, 13]. In the present study, the clinical signs noticed within 12 hours after a high dose of acetaminophen. The most common clinical signs reported in cats with acetaminophen toxicity were mental depression, weakness, tachycardia, tachypnoea or dyspnoea, ataxia, anorexia, vomiting, salivation, diarrhoea, pale/muddy mucous membrane, swollen face and paws, dark brown urine, coma and death (Aroson and Drobatz, 1996; Richardson, 2000) [3, 12]. The swollen or oedematous face might be due to vasculitis (Alwood, 2009) [2]. The dark brown color of the urine was most consistent with methemoglobinuria due to methemoglobin formation and haemolysis (Allen, 2003) [1]. The clinical signs observed in the present study were in agreement with early researchers.

Erythrocytes were more susceptible to NAPQI in cats. NAPQI caused severe oxidative stress to red blood cells leading to oxidation of ferrous iron to ferric iron which converted haemoglobin to methemoglobin (Richardson, 2000; Sellon, 2001) [12, 13]. Methemoglobinaemia was responsible for muddy or brown colour mucous membrane and was usually accompanied by tachycardia, tachypnoea, weakness and lethargy. Heinz bodies were formed from the precipitation of damaged haemoglobin within the red blood cells and lead to increased osmotic fragility of RBCs and haemolytic anaemia (Aroson and Drobatz, 1996) [3]. Moderate anaemia in the present case might be because of Heinz body associate haemolytic anaemia. Centrilobular necrosis was the most common hepatocellular damage seen in acetaminophen toxicity (Richardson, 2000) [12]. The elevated ALT, ALP, total billirubin level in the present study might be due to direct effect of NAPQI on the hepatocytes to cause hepatocellular damage and haemolytic anaemia. Large dose of acetaminophen could cause nephrotoxicity due to proximal tubular necrosis (Golstein and Schnellmann, 1996) [5]. Elevated blood urea nitrogen and creatinine in the kitten might be associated with renal damage. The diagnosis of acetaminophen toxicity was mostly base upon exposure history and developed clinical signs. Induction of emesis and gastric lavage would be effective if the animals presented within one hour of ingestion of acetaminophen. Gastric decontamination with activated charcoal @ 1-3 g/kg would be effective within two hours and would help to absorb acetaminophen but it should be repeated, since acetaminophen undergoes enterohepatic circulation. In the present study, the kitten was presented after 12 hours of ingestion (Richardson, 2000) [12]. Hence, induction of emesis, gastric lavage and administration of activated charcoal were not attempted. The principal treatment and antidote for acetaminophen toxicity was N-acetylcystine (NAC). NAC attached with acetaminophen metabolites (NAPQI) to make them inactive and served as a glutathione precursor. NAC could reduce the liver damage or methemoglobinuria by providing alternate substrate for conjugation. NAC was administered orally as 5% solution to cats at an initial loading dose of 140 mg/kg, then 70 mg/kg every 6 hours for 7 total treatments (Oehme, 1986; Aroson and Drobatz, 1996; Plumb, 1999; Pothiappan *et al*., 2014) [7, 3, 10, 11]. Ascorbic acid (@ 30 mg/kg q 6-12 h po or iv) provided a reserve system for reduction of methemoglobin to haemoglobin (Perry, 1997). S-adenosyl-methionine was also precursor of glutathione, reducing methemoglobin to haemoglobin and reduced the liver toxicity (Terneus *et al*., 2008) [15]. In the present study, kitten with acetaminophen toxicity was successfully treated with N-acetylcystine, ascorbic acid, S-adenosyl methionine as described by the earlier researchers.

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Fig 1: Kitten with acetaminophen toxicity - Facial swelling

Table 1: Hamatobiochemical values of kitten with acetaminophen toxicity

S. No.	Parameters	Observed values in kitten	Reference values (Silverstein and Hopper, 2009)
1.	Haemoglobin (g/dl)	8.4	10.6 – 15.6
2.	Packed cell volume (%)	28	31.7 – 48.0
3.	Red blood cells (x10^6/cumm)	5.2	6.5 – 11.2
4.	White blood cells (x10^3/cumm)	7.6	4.0 – 18.7
5.	Alanine aminotransferase (IU/L)	192	32 – 152
6.	Alkaline phosphatase (IU/L)	126	28 - 87
7.	Total billirubin (mg/dl)	1.2	0.1 – 0.8
8.	Blood urea nitrogen (mg/dl)	87	15 – 32
	Creatinine (mg/dl)	2.8	1.0 – 2.0

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