Nimesulide-induced acute biliary tract injury and renal failure in a kitten: a case report

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ABSTRACT: A 3-month-old male kitten was presented to our clinic with malaise, vomiting and jaundice. In the anamnesis, we learned that the cat had a history of anorexia, sneezing, and nasal discharge and that the owner had administered 100 mg/day (t.i.d.) nimesulide orally for three days. In the laboratory study, high levels of serum alkaline phosphatase, γ-glutamyl transtransferase, total bilirubin, direct bilirubin, indirect bilirubin, urea, and creatinine were detected. All the clinical signs and laboratory abnormalities returned to normal levels after cessation of the nimesulide and supportive treatment. In this case, clinical and laboratory findings were thought to be compatible with nimesulide-induced acute biliary injury and renal failure. This case report indicates that the household pets are at risk of toxic drugs administered by their owners and great caution should be taken in administering NSAIDs in cats.

Keywords: nonsteroidal anti-inflammatory drug; nimesulide; biliary injury; renal failure; kitten

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most popular classes of drugs with anti-inflammatory, analgesic, and antipyretic effects (Thawani et al., 2003; Lacroix et al., 2004). The use of NSAIDs have recently increased in small animals. This has resulted in a greater incidence of acute and chronic NSAID toxicities (Jones et al., 1992; Vollmar, 1993). Xavier and Kogika (2002) reported that NSAID induced poisoning rates are 86.4% and 50.0% in drug induced toxicities in dogs and cats respectively.

Nimesulide is a relatively new NSAID, and is popular because it causes less gastrointestinal side-effects compared with other non-selective NSAIDs in humans (Hawkey, 1999). Nimesulide has been widely prescribed in humans in about 50 countries including Italy, Switzerland, Belgium, Mexico, Brazil, and Turkey (Merlani et al., 2001). On the basis of its use in humans, nimesulide has been administered to household animals, especially dogs (Ramesh et al., 2001).

Instances of hepatic and renal injury have been reported for most NSAIDs (Rabinovitz and Von Thiel, 1992; Weiss et al., 1999). The use of nimesulide may precipitate a mild rise in serum liver enzyme levels (Pasquale et al., 1993), though few cases where nimesulide has been responsible for fatal liver and renal failure have been reported in humans (Schattner et al., 2000). Ramesh et al. (2001) has stated that 2 mg/kg nimesulide caused gastric ulcers and mild nephrotoxicity to develop in dogs in four days. To the authors' knowledge, there is no cited case of a cat suffering from nimesulide-induced hepatic and renal injury. In this report, we presented the case of a kitten with acute biliary injury and renal failure caused by nimesulide.

Case history

A 3-month-old mixed breed male kitten weighing 350 g was presented with suffering from malaise,

vomiting, and jaundice. The anamnesis revealed that the cat had a history of anorexia, sneezing, and nasal discharges and that the owner had administered to the cat a total of 100 mg/day nimesulide (Nimes® 100 mg Tablet; Sanovel) orally divided into three doses for three days. The hematological findings were as follows; erythrocytes 3.93×10^6/ml, leucocytes 7.2×10^3/ml, hemoglobin 17.2 mg/100 ml, hematocrit 28%, neutrophils 66%, lymphocytes 26%, monocytes 6%, eosinophil 2%. The results of the serum biochemical analysis described the following levels; aspartate aminotransferase (AST) 38 IU/l, alanine aminotransferase (ALT) 57 IU/l, alkaline phosphatase (ALP) 248 IU/l, γ-glutamyl transtransferase (GGT) 110 IU/l, total bilirubin 6.5 mg/100 ml, direct bilirubin 4.8 mg/100 ml, indirect bilirubin 1.7 mg/100 ml, urea 280 mg/100 ml and creatinine 7.6 mg/100 ml were detected. In the analysis of urine a pH of 6.5, density 1 047, bilirubin (3+) and protein (3+) were found. The ultrasonographic examination detected hyperecogenity in the gall bladder and in the bile duct walls. Laboratory and ultrasounographic results revealed acute biliary injury and renal failure with high levels of alkaline phosphatase, γ-glutamyl transferase, bilirubin, urea and creatinine. Intravenous fluids (lactated ringer and glucose 5%), antiemetic (metaclopromide, 1 mg/kg) and an inhibiter of H_2 receptors (ranitidine, 1 mg/kg) were administered as supportive treatment. Following treatment, appetite began to improve on the 3rd day. On Day 10, physical examination revealed nothing out of the ordinary and the cat was discharged. Liver and renal function tests findings returned to normal values one month after cessation of the nimesulide treatment (Table 1).

DISCUSSION

Drug induced liver injury is a potential complication of most drug therapies as the liver has a central metabolic role for various drugs (Lacroix et al., 2004). Most of the NSAIDs have been reported to provoke hepatic and renal injury (Gay, 1990; Rabinovitz and Von Thiel, 1992). Nimesulide is a preferred cyclooxygenase-2 (COX-2) inhibiter, favoured because of the lower amount of gastrointestinal side-effects it causes compared with other non-selective NSAIDs (Hawkey, 1999). Nimesulide has been associated with adverse reactions in the liver, including increases in serum aminotransferase activities, hepatocellular necrosis, and/or intrahepatic cholestasis (Boelsterli, 2002). Many cases of nimesulide induced hepatotoxicity and renal failure have been reported in humans (Apostolou et al., 1997; Sbeit et al., 2001). A wide range of liver injuries ranging from asymptomatic elevated liver function enzymes (Pasquale et al., 1993) to fatal acute hepatic and renal failure (Schattner et al., 2000) have been reported. The sale of nimesulide has been suspended in some European countries because of these toxic effects. The European Union has also issued precautionary advice on the marketing of this drug following serious complications after its use (Thawani et al., 2003).

The molecular mechanisms underlying nimesulide-induced toxicity have not yet been fully understood. However, experimental evidence suggests that nimesulide induces the formation of reactive metabolites in the hepatobiliary compartment that covalently modify proteins, produce oxidative stress, and cause mitochondrial injury. Genetic factors and individual sensitivity are no doubt important factors in the

Table 1. Serum biochemistry changes on Day 1, Day 10 and Day 30

Serum Biochemistry	Day 1	Day 10	Day 30
AST (IU/l)	38	31	30
ALT (IU/l)	57	68	39
ALP (IU/l)	248	115	70
GGT (IU/l)	110	40	7
Total bilirubin (mg/100 ml)	6.5	1.1	0.6
Direct bilirubin (mg/100 ml)	4.8	0.1	0.1
Indirect bilirubin (mg/100 ml)	1.7	1.0	0.5
Urea (mg/100 ml)	280	173	48
Creatinin (mg/100 ml)	7.6	1.7	1.3

etiology of these symptoms and determine whether this potential toxicity will become clinically manifest (Robin et al., 1997; Boelsterli, 2002). Van Steenbergen et al. (1998) stated that immunological and metabolic idiosyncratic reactions may be the pathogenic mechanisms of nimesulide-induced liver disease in humans. Renal adverse effects to these drugs are due to the inhibition of prostaglandin synthesis, an increase in renal vascular resistance with a concomitant decrease in diuresis, GFR, and renal blood flow acute reversible renal failure (Apostolou et al., 1997; Balasubramaniam, 2000; Prevot et al., 2004).

Merlani et al. (2001) has reported that the primary manifestation of nimesulide toxicity is jaundice. The average duration of the period before the onset of toxicity in published cases is 62 days (range 7–180 days), though a period as short as five days has been reported (Schattner et al., 2000; Merlani et al., 2001). In the present case, the cat was suffering from severe jaundice following intake of nimesulide for three days. This difference could be related to the high dose administered, the age of the animal, and the fact that cats are known to be susceptible to most drugs. Also, in the present case nimesulide toxicity might be associated with predisposition, duration of exposure time, or the use of a high dose.

We have reported a case, the first in a cat, of nimesulide-induced reversible acute biliary injury and renal failure in a three month old kitten. The present case indicates that pets are at a great risk of NSAID toxicosis administrated to them by their owners and great that great caution should be taken in administrating NSAIDs, including nimesulide, to cats.

REFERENCES

Apostolou T., Sotsiou F., Yfanti G., Andreadis E., Nikolopoulou N., Diamantopoulos E., Billis A. (1997): Acute renal failure induced by nimesulide in a patient suffering from temporal arteritis. Nephrology Dialysis Transplantation, 12, 1493–1496.

Balasubramaniam J. (2000): Nimesulide and neonatal renal failure. Lancet, 355, p. 575.

Boelsterli U.A. (2002): Mechanisms of NSAIDs-induced hepatotoxicity: focus on nimesulide. Drug Safety, 25, 633–648.

Gay G.R. (1990): Another side effect of NSAIDs. The Journal of the American Medical Association, 264, 2677–2678.

Hawkey C.J. (1999): COX-2 inhibitors. Lancet, 353, 307–314.

Jones R.D., Baynes R.E., Nimitz C.T. (1992): Nonsteroidal anti-inflammatory drug toxicosis in dogs and cats: 240 cases (1989–1990). Journal of the American Veterinary Medical Association, 201, 475–477.

Lacroix I., Lapeyre-Mestre M., Bagheri H., Pathak A., Montastruc J.L. (2004): Nonsteroidal anti-inflammatory drug-induced liver injury: a case – control study in primary care. Fundamental and Clinical Pharmacology, 18, 201–206.

Merlani G., Fox M., Oehen H.P., Cathomas G., Renner E.L., Fattinger K., Schneemann M., Kullak-Ublick G.A. (2001): Fatal hepatotoxicity secondary to nimesulide. European Journal of Clinical Pharmacology, 57, 321–326.

Pasquale G., Scaricabarozzi I., D'Agostino R. (1993): An assessment of the efficacy and tolerability of nimesulide vs. paracetamol in children after adenotonsillectomy. Drugs, 46, 234–237.

Prevot A., Mosig D., Martini S., Guignard J.P. (2004): Nimesulide, a cyclooxygenase-2 preferential inhibitor, impairs renal function in the newborn rabbit. Pediatric Research, 55, 254–260.

Rabinovitz M., Von Thiel D.H. (1992): Hepatotoxicity of nonsteroidal anti-inflammatory drugs. The American Journal Gastroenterology, 87, 1696–1704.

Ramesh N., Jayakuma K., Narayana K., Vijayasarathi S. K. (2001): Nimesulide toxicity in dogs. Indian Journal of Pharmacology, 33, 217–218.

Robin M.A., Le Roy M., Descatoire V., Pessayre D. (1997): Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. Journal of Hepatology, 26, 23–30.

Sbeit W., Krivoy N., Shiller M., Farah R., Cohen H.I., Struminger L., Reshef R. (2001): Nimesulide-induced acute hepatitis. The Annals of Pharmacotherapy, 35, 1049–1052.

Schattner A., Sokolovskaya N., Cohen J. (2000): Fatal hepatitis and renal failure during treatment with nimesulide. Journal of Internal Medicine, 247, 153–155.

Thawani V., Sontakke S., Gharpure K., Pimpalkhute S. (2003): Nimesulide: The Current Controversy. Indian Journal of Pharmacology, 35, 121–122.

Van Steenbergen W., Peeters P., De Bondt Staessen D., Buscher H., Laporta T., Roskams T., Desmet V. (1998): Nimesulide-induced acute hepatitis: evidence from six cases. Journal of Hepatology, 29, 135–141.

Vollmar A.M. (1993): Clinico-toxicologic aspects of nonsteroidal anti-inflammatory agents in the dog and cat. Tierarztliche Praxis, 21, 149–152.

Weiss P., Mouallem M., Bruck R., Hassin D., Tanay A., Brickman C.M., Farfel Z., Bar-Meir S. (1999):

Nimesulide-induced hepatitis and acute liver failure. Israel Medical Association Journal, 1, 89–91.

Xavier F.G., Kogika M.M. (2002): Common causes of poisoning in dogs and cats in a Brazilian veterinary teaching hospital from 1998 to 2000. Veterinary and Human Toxicology, 44, 115–116.

Received: 2006–10–30
Accepted after corrections: 2008–02–02

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