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What is This?

Successful treatment of hepatic failure secondary to diazepam administration in a cat

Fiona M Park

Abstract

A 2-year-old castrated male domestic shorthair cat developed acute hepatic failure following oral diazepam administration for behavioral problems. The patient survived with intensive supportive care and was discharged after 5 days in hospital. Successful treatment of diazepam-associated fulminant hepatic failure in cats has rarely been described in the veterinary literature.

A 2-year-old, castrated male, domestic shorthair cat was presented to the Ontario Veterinary College Health Sciences Centre (OVC-HSC) for depression, anorexia and acute hepatic failure.

The cat had a 1-year history of inappropriate urination and aggressive behavior directed towards another cat in the household. There had been no response to environmental modification or feline pheromone use. A complete blood count (CBC) and biochemistry profile performed by the referring veterinarian 2 weeks prior to presentation showed no significant abnormalities. The cat was started on diazepam (0.31 mg/kg PO q12h) at that time. The dose was increased to 0.62 mg/kg PO q12h, 5 days later. Five days following the dose increase, anorexia developed and diazepam administration was discontinued.

Two weeks after diazepam administration was started, a serum biochemical profile showed marked hyperbilirubinemia [total bilirubin 78 µmol/l; reference interval (RI) 0–4.5 µmol/l], markedly elevated alanine aminotransferase (ALT) activity (2225 U/l; RI 5–110 U/l), moderately elevated aspartate aminotransferase (AST) activity; (335 U/l; RI 5–71 U/l) and mildly elevated alkaline phosphatase (ALP) activity (130 U/l; RI 10–85 U/l). Serum blood urea nitrogen (BUN) and albumin were within reference intervals.

On presentation to the OVC-HSC, the cat was dull, recumbent and minimally responsive to stimuli. His menace response was absent bilaterally. The cat was hypothermic (rectal temperature 36.3°C), tachypneic (80 breaths per min) and was estimated to be 7–8% dehydrated. The mucus membranes were icteric. A grade III/VI left parasternal early systolic heart murmur was detected; lung sounds were normal. The systolic blood pressure was within normal limits (148 mmHg).

The packed cell volume (PCV) and total solids (TS) were mildly elevated, consistent with dehydration (PCV 50 % and TS 8.2 g/l). The prothrombin time (PT) was mildly prolonged and the activated partial thromboplastin time (aPTT) was markedly prolonged (PT 23 s; RI 15–22 s and aPTT 222 s; RI 65–119 s). The plasma ammonia level was mildly elevated (77 mmol/l; RI 0.0–60.0 mmol/l). Venous blood gas and electrolyte analysis was unremarkable aside from moderate hypokalemia (3.0 mmol/l; RI 3.6–5.2 mmol/l). Urine culture was negative for bacterial growth. Thoracic radiographs were unremarkable. An echocardiogram revealed no evidence of structural cardiac disease. An abdominal ultrasound did not reveal any abnormal findings except for an enlarged hepatic lymph node; the hepatic size and echogenicity were considered normal. A jugular catheter was placed to facilitate blood sampling. The cat was rehydrated with intravenous crystalloid fluids (0.9% sodium chloride) supplemented with potassium chloride (20 mEq/l). In addition, 85 ml of type A fresh frozen feline plasma was given intravenously. The patient was rewarmed with a forced-air warming blanket (Bair Hugger; Arizant Healthcare, Eden Prairie, MN, USA).

Treatment for hepatic failure was also started at admission, including lactulose (Euro-pharm, Montreal, QC, Canada) 2.5 ml PO q8h, metronidazole (Hospira, Lake Forest, IL, USA) 7.5 mg/kg IV q12h and vitamin K_1 (Vétoquinol, Lure, France) 2 mg/kg SC q12h for three

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doses. N-acetylcysteine (Sandoz, Holzkirchen, Germany) 140 mg/kg IV initial dose, followed by 70 mg/kg IV q8h, and S-adenosylmethionine (Zentonil Plus; Vétoquinol) 200 mg PO q24h were also administered. Other supportive care included metoclopramide (Sandoz) 2 mg/kg/day IV constant rate infusion (CRI), and famotidine (Omega, Birmingham, AL, USA) 0.5 mg/kg IV q12h. A nasoesophageal feeding tube was placed and enteral feeding was provided as a CRI starting at one half of calculated resting energy requirements (4 ml/h, Clinicare canine/feline liquid diet; Abbott Laboratories, Abbott Park, IL, USA). This was gradually increased to full resting energy requirements over the following 2 days.

The day following admission, the cat remained dull and hypothermic, although his plasma ammonia level had normalized (29 mmol/l). He was found to be hypotensive (systolic pressure 64 mmHg); treatment with a crystalloid bolus (10 ml/kg) temporarily restored normal blood pressure. Following a second episode of hypotension, a pentastarch CRI was started (Pentaspan 10%; Bristol-Myers Squibb, New York, NY, USA) 10 ml/kg/day IV; the cat remained normotensive following this. As a result of persistent hypokalemia, the concentration of potassium chloride supplementation in the crystalloid fluids was progressively increased to 100 mEq/l.

Four days after admission, a repeat biochemistry profile showed significant improvement in the hyperbilirubinemia and hepatic enzyme activities (total bilirubin 22 U/l; RI 0.0–3.0 U/l, ALT 416 U/l; RI 31–105 U/l, ALP 168 U/l; RI 16–113 U/l). However, hypoalbuminemia (28 g/l; RI 30–44 g/l) and decreased BUN (2.5 mmol/l; RI 6.0–12.0 mmol/l) were present—consistent with hepatic synthetic failure. The PT was within normal limits; however, aPTT remained prolonged (37 s; RI 12–25 s). Mild hypokalemia was persistent, so spironolactone was started (Aldactone; Pfizer, New York, NY, USA), 6.25 mg PO q12h.

Five days after admission, the cat's mentation appeared normal, his appetite had returned and he was discharged into the care of his owners. S-adenosylmethionine (100 mg PO q24h), lactulose (2.5 ml PO q12h), potassium gluconate (2 mEq PO q12h) and spironolactone (6.25 mg PO q12h) were continued at home.

Two weeks following discharge the cat was re-examined at the OVC–HSC. The owners reported that his appetite was now normal and no significant abnormalities were detected on physical examination aside from the previously detected heart murmur. The cat's liver enzyme activities were within reference intervals; however, mild hyperbilirubinemia was still present (6 μmol/l; RI 0.0–3.0 μmol/l). Serum potassium was within normal limits (4.4 mEq/l). It was not possible to collect an adequate jugular venous blood sample to repeat coagulation testing. Spironolactone, potassium gluconate and lactulose were discontinued. Two months following discharge the cat was still doing well at home, and S-adenosylmethionine was discontinued.

Diazepam is a benzodiazepine derivative that has been prescribed in cats for its anxiolytic, muscle relaxant, sedative, anticonvulsant and appetite stimulant effects.[1] The mode of action is via binding to γ-aminobutyric acid (GABA) receptors in the central nervous system (CNS) and potentiating of GABA-mediated neural inhibition.[2]

Diazepam-associated hepatotoxicity has been reported in one post mortem and one clinical case series in cats ranging from 1–12 years of age.[3,4] Typical clinical signs include anorexia and lethargy starting 7–13 days following oral diazepam administration. Diazepam doses ranged from 0.3–0.8 mg/kg/day. In all cases, marked elevations of ALT activity, mild to moderate elevations of ALP activity, and moderate hyperbilirubinemia were present. Coagulation times (PT and aPTT) were prolonged in all cases in which they were measured. Elevated fibrin degradation products, thrombocytopenia and hypofibrinogenemia were also reported in some cases.[4] Liver histology typically revealed a mixed pattern consisting of severe acute to subacute lobular to massive hepatic necrosis with mild-to-moderate cholestasis. The surviving cat in the clinical case series had less pronounced hepatic necrosis than the non-surviving cases.[4] This cat received enteral feeding, intravenous crystalloid fluid therapy, water-soluble vitamins, ampicillin and vitamin K_1.[4] The non-surviving cats received various combinations of these treatments, in addition some also received blood product transfusions and lactulose.[4]

The cat in this case report presented with clinicopathologic test results consistent with an acute hepatopathy and neurologic abnormalities suggestive of hepatic encephalopathy. The fact that the serum biochemistry profile was unremarkable immediately prior to benzodiazepine administration is supportive of diazepam-associated acute hepatic failure. However, a liver biopsy was not performed to characterize the histologic abnormalities. Differential diagnoses for this cat's prolonged PT and aPTT at admission include disseminated intravascular coagulation (DIC) or failure of hepatic synthesis of coagulation factors. Fresh frozen plasma was given to replenish coagulation factors. On later testing, aPTT remained prolonged, though less markedly, and the PT was normal. Differential diagnoses for the persistent prolonged aPTT include factor XII deficiency, unresolved DIC or laboratory error. Unfortunately, a blood sample could not be obtained at the recheck examination to recheck the aPTT or perform factor XII measurement. The cat's ALT and ALP activities had normalized by 2 weeks following discharge from the OVC-HSC; however, it is not known whether chronic hepatitis will develop over time. It has been reported that biopsy of one cat's liver 1 year after recovery from diazepam-associated hepatic failure demonstrated no residual inflammation or fibrosis.[5]

Diazepam-associated fulminant hepatic failure is suspected to be an idiosyncratic reaction because of the rarity with which it is reported in cats, and that

the affected cats have usually received doses within the recommended range.[1,4–6] The mechanism of hepatotoxicity is not known; however, accumulation of a toxic intermediate causing zonal necrosis has been proposed.[4] Benzodiazepines are also an occasional cause of hepatotoxicity in human patients.[7–9] Metabolism of diazepam occurs in the liver via N-dealkylation or hydroxylation to desmethyldiazepam (nordiazepam), temazepam and oxazepam — all of which are pharmacologically active.[1,4] These lipophilic metabolites are conjugated with glucuronide, then excreted in the urine. Glucuronidation is catalyzed by hepatic microsomal UDP-glucouronosyltransferase (UGT) enzymes.[10] Cats are sensitive to the adverse effects of many drugs and toxins that require glucuronidation before elimination.[10] Their deficiency in acetaminophen glucuronidation has been shown to be caused by multiple mutations in the UGT1A6 gene.[10] The hepatic UGT isoform that performs glucuronidation of benzodiazepines has not been identified.[10] However, a defective gene could be present in certain cats, delaying excretion of diazepam and its metabolites and leading to hepatotoxicity.

Diazepam administration to rodents has been shown to lead to oxidative damage[11,12] and intracellular calcium accumulation.[11] Pretreatment with antioxidants including vitamin E[11], selenium,[11] or vitamin C[12] was shown to attenuate these lesions. In this case, S-adenosylmethionine and N-acetylcysteine were given to increase hepatic glutathione levels and support the liver's own antioxidant capacity.[1] Lactulose was also administered as a treatment for hepatic encephalopathy. Lactulose causes acidification of colonic contents resulting in ammonia trapping and decreased absorption.[13] This cat was also treated with metronidazole to reduce urease-producing intestinal bacterial numbers. However, the efficacy of antimicrobials for treatment of hepatic encephalopathy has not been proven in veterinary medicine.[13]

This patient had persistent hypokalemia despite high rates of intravenous potassium supplementation. The aldosterone antagonist spironolactone was administered to attempt to address any secondary hyperaldosteronism contributing to the hypokalemia. Stimulation of the renin-angiotensin-aldosterone system has been shown to occur in fulminant hepatic failure.[14] In this case, treatment with spironolactone was started once the cat was rehydrated and hypotension had resolved.

The majority of reported cases of feline diazepam-associated hepatotoxicity have not survived.[3–6] This cat was within the age range of previously reported cases and received a similar duration of diazepam therapy prior to presentation. However, the dose of diazepam given following the dose increase was higher than previous cases.[3,4] The treatment that this cat received did not differ markedly to that previously reported,[4] except for the addition of S-adenosylmethionine and N-acetylcysteine. These treatments may have significantly influenced this cat's outcome, or there may have been a lesser degree of hepatic necrosis than typical for this toxicity. This case shows that there is a population of cats with diazepam-associated hepatic necrosis that may survive with appropriate treatment. In addition, the treatment principles described here also apply to cats with acute hepatic failure due to other causes.

Conflict of interest The author declares that there is no conflict of interest.

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