Blindness now attributed to enrofloxacin therapy in a previously reported case of a cat with acromegaly treated by cryohypophysectomy

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A case of feline acromegaly was successfully treated by cryosurgical ablation of the pituitary gland (1). Unfortunately, abrupt resolution of insulin-resistant diabetes mellitus 2 mo postoperatively resulted in a hypoglycemic crisis due to insulin overdose. The crisis was characterized clinically by hypothermia, coma, seizures, and constricted, nonresponsive pupils. The cat's condition stabilized over 24 h, but it had become blind, in addition to having poor physiologic nystagmus and proprioceptive deficits, and, 1 mo later, aggressive behavioral changes. Blindness during this early period was attributed to acute cerebral cortical necrosis. Neurologic deficits other than behavioral changes resolved over 3 mo, but the cat remained blind for the next 9 mo, at which time it was euthanized. Blindness during this later period was attributed to retinal degeneration based on clinical findings, electroretinography, and, ultimately, histopathologic findings. The retinal degeneration was unexplained in the original report (1). The purpose of this report is to provide additional details of the case, including therapy with enrofloxacin (Baytril; Bayer, Toronto, Ontario), which, we now believe, was responsible for the retinal degeneration and permanent blindness. The day of insulin overdose is referred to as day 0.

Pupillary light reflexes were normal by day 3. No abnormalities were noted on a complete ophthalmologic examination on day 7, other than an absent menace response; however, the cat did orient and respond to bright light, suggesting that it was not completely blind. On day 17, the cat could negotiate an obstacle course, had some following eye movements, and would orient towards minimally odiferous, isolated objects placed in its path. The consensus was that the cat had definitely regained some vision, but progressive improvement beyond that time was not observed. On day 45, persistent pupillary dilation was noted. Ophthalmologic examination revealed bilateral retinal degeneration, characterized by absent pupillary light reflexes, tapetal hyperreflectivity, optic nerve atrophy, and attenuation of retinal vessels. There was no activity on an electroretinogram. Findings were similar prior to euthanasia.

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On histopathological examination of the eyes, lesions were restricted to the retina. There was complete photoreceptor atrophy and loss of the outer nuclear layer, with retention of the inner nuclear layer and ganglion cells. The optic chiasm and optic tracts had widespread vacuolation and widely scattered axonal necrosis, indicating that cryoinjury to these tissues had occurred at the time of cryohypophysectomy. However, the optic nerves, nerve fiber layer, and ganglion cells were normal, indicating that degeneration of the outer retinal layer was not a result of a "dying-back" process from previous cryoinjury to the optic tracts (1).

A problem not discussed in the original report was urinary retention and urinary tract infection. The cat did not urinate well for approximately 6 wk following day 0, and developed a large, flaccid bladder. This was managed with indwelling and intermittent urethral catheterization, as well as with bethanecol (Urecholine; Frosst, Kirkland, Quebec), 0.5 mg/kg bodyweight (BW), q8h, from days 16 to 21. Urethral catheterization resulted in recurrent and resistant urinary tract infections with *Escherichia coli* and *Enterobacter aerogenes*. Pyelonephritis was suspected on the basis of an elevated serum creatinine level (193 μmol/L; reference range 75 to 180 μmol/L) and an inappropriately low urine specific gravity of 1.024. The urinary tract infection was treated at different times with amoxicillin (Moxilean; Bimeda-MTC Animal Health, Cambridge, Ontario), 20 mg/kg BW, PO, q8h; amoxicillin-clavulanate (Clavamox; Ayerst Veterinary Laboratories, Guelph, Ontario), 25 mg/kg BW, PO, q12h; and trimethoprim-sulfadiazine (Tribrissen; Schering Canada, Pointe-Claire, Quebec), 18 mg/kg BW, PO, q12h. Treatment with enrofloxacin was then started on day 37. The initial dosage prescribed by the attending clinician was 68 mg, PO, q8h, representing a daily dose of 40 mg/kg BW (It is acknowledged that this dose is well above the label dosage at the time (January 1991, 2.5 mg/kg BW, q12h), and above the label dosage change in July 1997 (5 to 20 mg/kg BW/d)). The dosage was reduced to 68 mg, PO, q12h (daily dose 27 mg/kg BW), 4 d later (day 41), and further reduced to 23 mg, PO, q12h (daily dose 9 mg/kg BW), 2 d after that (day 43). Enrofloxacin was continued at 23 mg, PO, q12h, for another 34 d. Urine cultures during the enrofloxacin therapy, 6 wk after discontinuing the therapy, and prior to euthanasia were negative. Chronic renal failure did not develop. Histopathologic findings in the kidney were consistent with chronic pyelonephritis.

Another problem not discussed in the original case report was hepatopathy attributed to phenobarbital. Phenobarbital (Phenobarbital; Parke-Davis, Scarborough, Ontario), 2 mg/kg BW, PO, q12h, was given to control seizures, beginning on day 10. On day 33, the alanine aminotransferase (ALT) level was elevated at 917 U/L (reference range, 10 to 75 U/L), in contrast to 51 U/L 2 d prior to beginning the phenobarbital treatment. The phenobarbital level was 145.51 μmol/L, well within the therapeutic range (65 to 172 μmol/L). Hepatic failure did not occur, based on a normal serum bilirubin level and an ammonia tolerance test. The phenobarbital treatment was rapidly tapered over 4 d, and was discontinued on the day that the enrofloxacin therapy began. The phenobarbital level 1 wk later (day 44) was 25.32 μmol/L and the ALT level 2 wk later (day 51) was normal at 65 U/L. Therapy with diazepam (Valium; Hoffman-LaRoche, Mississauga, Ontario), 0.5 mg/kg BW, PO, q12h, was started concurrently with enrofloxacin and continued for 15 d.

A final previously unreported problem was idiopathic constipation, diagnosed prior to the onset of diabetes mellitus. This had been treated over a period of time with lactulose (Acelac; Technilab, Mirabel, Quebec), 2 to 3 mL added to 3 or 4 daily meals.

Although this cat had had numerous problems and had been treated with numerous drugs, the retinal degeneration could not be satisfactorily explained at the time of the original report. We hypothesized that it might have been a case of sudden acquired retinal degeneration (SARD), although, to our knowledge, at that time and since then, a case of feline SARD has not been documented. A toxic insult to the retinas was considered, but none of the drugs used in this cat had been associated with retinopathy at that time. However, the association of enrofloxacin and visual disturbances in cats is now firmly established. In a letter circulated to Canadian veterinarians, dated July 6, 2000, Bayer Inc. reported an accumulating number of anecdotal reports of visual impairment following the use of Baytril in cats. This prompted further investigations where normal cats were treated with enrofloxacin at doses ranging from 5 to 50 mg/kg BW for 21 d. In a subsequent letter, dated April 10, 2001, Bayer Inc. reported, "The administration of enrofloxacin at 20 mg/kg body weight or greater resulted in mild to severe retinal degeneration, abnormal electroretinograms, and microscopic changes in the retina." Detailed results of the toxicity study are to be published in the future (personal communication, Kathleen Keil, Bayer Inc.).

The first report of a clinical study of enrofloxacin-associated retinal degeneration was published recently (2). In this study, daily doses of enrofloxacin in 16 cats ranged from 6 to 54 mg/kg BW; 1 cat was treated at 4.6 mg/kg BW. The onset of visual disturbances was observed in from 2 d to more than 12 wk; it occurred in less than 10 d in at least 7 cats. Most cats had permanent blindness. The eyes of 1 blind cat were examined histologically — lesions included diffuse retinal degeneration affecting the outer nuclear and photoreceptor layers, while the inner retinal layers were preserved to some extent.

With our case, a high dose of the drug had been given for 8 d prior to the retinal degeneration being detected. Marginal renal dysfunction may have further increased the plasma levels of the drug. The rapid onset of blindness is consistent with that observed in the above mentioned study (2) and in other presumptive cases of enrofloxacin-induced blindness collectively seen by the authors. Furthermore, following a toxic insult to the retina, the appearance of ERG changes within the time frame seen in this case is also expected. Finally, the histopathologic lesions in the previously reported case (2) and in our case were similar.

In conclusion, in the absence of another explanation, it appears that the use of enrofloxacin was responsible for the retinal degeneration and contributed to the permanent blindness that developed in our case. Although visual disturbances following the use of enrofloxacin at the currently recommended daily dose of 5 mg/kg BW in cats appear to be rare, the high dose of the drug that was used in our case is now known to cause retinal degeneration. Enrofloxacin-induced retinal degeneration is occasionally reversible (2), but the prolonged course of therapy at the dosage used in this cat would have probably eliminated the possibility of it occurring. The effect, if any, of concurrent phenobarbital and diazepam blood levels on the retinal toxicity of enrofloxacin is not known.

References

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