Retinopathy associated with ivermectin toxicosis in two dogs

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Case Description—Two dogs (dogs 1 and 2) were examined for sudden onset of blindness. Both dogs had mild obtundation and mydriasis in both eyes. It was thought that dog 1 may have ingested ivermectin; dog 2 had been treated with ivermectin for demodicetic mange.

Clinical Findings—On initial examination, both dogs had mydriasis and decreased pupillary light reflexes in both eyes. Dog 1 had an absent menace response bilaterally. Fundic examination of both eyes in both dogs revealed regions of multifocal retinal edema and folds with low-lying retinal separation. The electroretinogram was extinguished in dog 1 and attenuated in dog 2. Ivermectin was detected in serum samples from both dogs.

Treatment and Outcome—Both dogs made a complete clinical recovery following cessation of exposure to ivermectin; electroretinographic findings improved, and retinal edema resolved with some residual chorioretinal scarring.

Clinical Relevance—To our knowledge, this is the first report of resolution of retinal edema and electroretinographic changes associated with ivermectin toxicosis in dogs. In dogs that develop blindness suddenly, fundic examination, electroretinography, and assessment of serum ivermectin concentration are diagnostically useful, even if exposure to ivermectin is unknown. (J Am Vet Med Assoc 2008;233:279–284)

A 1-year-old 14.5-kg (31.9-lb) neutered female Border Collie (dog 1) was evaluated at the Veterinary Medical Teaching Hospital of the University of California, Davis, because of mild obtundation and sudden onset of blindness of <1 day’s duration. General physical examination findings were unremarkable. Neurologic examination revealed mild obtundation and mydriasis in ambient light, lack of menace response and dazzle reflex, and sluggish and incomplete PLRs in both eyes. Anisocoria was not evident. The dog behaved as if unsighted, except for recognition of large objects in photopic conditions. In both eyes, palpebral reflexes were complete and globe position and movements were normal. Results of assessment of all cranial nerves (except for cranial nerve II), gait, postural reactions, segmental reflexes, and palpation of the vertebral column were considered normal.

A complete ophthalmic examination involving slit-lamp biomicroscopy and binocular indirect ophthalmoscopy was conducted. Both eyes were open and appeared comfortable. There was no overt ocular discharge or facial asymmetry. Other than a subtle posterior subcapsular cataract in the left eye, no abnormalities were detected in the anterior segment or vitreous humor of either eye. Fundic examination revealed approximately symmetric findings in both eyes. These abnormalities consisted of multifocal, indistinct, white-gray, vermiform to punctate, and occasionally branching opacities within the neurosensory retina. These lesions were diagnosed as retinal edema and folds (Figure 1). At times, these opacities seemed to be associated with the major retinal vessels and areas of suspected low-lying retinal separation. In other areas, the lesions were not raised, had more distinct margins suggestive of chronicity, and were more consistent with chorioretinal scars. All retinal opacities were located within a broad horizontal band at the tapetal-nontapetal border on both sides of the optic nerve head. The optic nerve head, tapetum, and retinal vasculature appeared normal in both eyes. Five months earlier, dog 1 had been assessed for an unrelated reason, and although there was no record that a fundic examination was performed at that time, direct and consensual PLRs were reported as normal. On the basis of the obtundation and funduscopic abnormalities, bilateral prechiasmal and diffuse or multifocal intracranial disease were indicated neuroanatomically. The primary differential considerations were infectious, inflammatory, toxic, or metabolic causes.

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ERG</td>
<td>Electroretinography</td>
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<tr>
<td>GABA</td>
<td>γ-Aminobutyric acid</td>
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<tr>
<td>LC-MS</td>
<td>Liquid chromatography-mass spectroscopy</td>
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<tr>
<td>m/z</td>
<td>Mass-to-charge ratio</td>
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<td>PLR</td>
<td>Pupillary light reflex</td>
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diagnosis of ivermectin toxicosis was suspected because of the potential exposure to ivermectin via ingestion of horse feces or spilled ivermectin paste. The day after the initial evaluation (2 days after presumed exposure), serum was obtained from the dog for ivermectin analysis via LC-MS. In brief, 1 g of serum was weighed into a glass tube, 4 mL of acetonitrile was added, and the tube was shaken vigorously by hand for approximately 1 minute. The tube was centrifuged, and 3 mL of the supernatant was transferred to a second glass tube. The supernatant was evaporated to dryness under nitrogen and reconstituted in 0.30 mL of methanol. Ten microliters of the extract was injected onto a high-pressure liquid chromatography equipped with a C18 monolith column. The isocratic mobile phase consisted of 12% of 10mM ammonium acetate in 0.1% aqueous formic acid and 88% of 10mM ammonium acetate with 0.1% formic acid in methanol at a flow rate of 1.0 mL/min. The high-pressure liquid chromatography system was interfaced to a mass spectrometer that was operated in selective reaction monitoring mode. The ammonium adduct of ivermectin B, at m/z 892 was fragmented at a collision energy of 35 V. The product ion at m/z 369 was used for quantitation, whereas a second fragment ion at m/z 307 was used as a confirmatory ion. Five-point calibration curves were derived for ivermectin fortified in negative control serum extract and were used to determine analyte concentrations in serum. The method detection limit for ivermectin in serum was estimated at 50 ng/g (50 ppb). The serum ivermectin concentration for dog 1 was 1,040 ng/g, confirming exposure to ivermectin. No specific treatment was initiated because the dog appeared to be clinically improving. Serum ivermectin concentration was rechecked 3 days after presumed exposure, at which time it was 491 ng/g. Two days after the initial evaluation (4 days after presumed exposure), the dog had appropriate mentation and menace responses and PLRs were improving. The dog was discharged from the hospital.

Seven days after the initial evaluation, dog 1 was reexamined. The owner reported improvement of the dog’s vision at home and considered its vision near normal at the time of examination. Results of physical and neurologic examinations were unremarkable. A complete ophthalmic examination was repeated. Resting pupil diameter was considered appropriate for the ambient light, and there was no anisocoria. Direct and consensual PLRs were brisk and complete in both eyes. In both eyes, dazzle and palpebral reflexes were complete and globe position and movements and menace response were normal. The dog behaved as if sighted in photopic conditions. No new abnormalities were detected in the anterior segment or vitreous humor in either eye. A fundic examination (conducted after pupil dilation was induced with topical application of tropicamide) revealed normal appearances of the optic nerve head, tapetum, and retinal vasculature in each eye. The multifocal retinal folds, edema, and low-lying separations detected previously were largely resolved; those affected regions had a slightly mottled, mosaic, or watermarked appearance (Figure 1). Electroretinography was repeated by use of the same protocol as used previously. The b-wave amplitudes were within expected range, 46 to 320 U/L). Urinalysis revealed moderate numbers of triple phosphate crystals, but findings were considered normal. Abnormalities were not detected via thoracic radiography. Abdominal ultrasonographic findings included moderate splenomegaly and reexamined. The owner reported improvement of the dog’s vision at home and considered its vision near normal at the time of examination. Results of physical and neurologic examinations were unremarkable. A complete ophthalmic examination was repeated. Resting pupil diameter was considered appropriate for the ambient light, and there was no anisocoria. Direct and consensual PLRs were brisk and complete in both eyes. 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The dog was genetically tested for the multidrug sensitivity mutation (mDR1-1Δ) in the MDR1 gene and did not carry the mutation.8

Ten months after initial presentation, the dog was reexamined. The dog was in good health and appeared normally sighted. Physical and neurologic examination findings were considered normal. Results of a complete ophthalmic examination confirmed that pupil sizes were appropriate and equal and that direct and consensual PLRs, menace response, dazzle and palpebral reflexes, and globe position and movements were normal in both eyes. Findings for the anterior segment and vitreous humor examination were unchanged in either eye. Fundic examinations of both eyes were conducted after pupil dilation with topical application of tropicamide; bilaterally, the optic nerve head, tapetum, and retinal vasculature were normal. However, a series of coalescing and overlapping, approximately circular, flat chorioretinal scars was detected along the tapetal-nontapetal border in both eyes. These scars were most prominent on the medial side of the optic nerve head in both eyes (Figure 1). In each eye, the remainder of the tapetal fundus appeared normal, whereas the remainder of the nontapetal fundus had a subtle mottled appearance. An ERG examination was repeated by use of the protocol used previously, and b-wave amplitudes were 166 µV in the right eye and 129 µV in the left eye.

An 8-month-old 12.3-kg (27.1-lb) spayed female Australian Cattle Dog cross (dog 2) was also examined at the hospital because of sudden onset of blindness. The dog had received a recommended dosage1 (600 µg/kg [272.7 µg/lb]) of 1% ivermectin solution orally once daily during the preceding 8-week period for treatment of demodicosis, without apparent adverse effects. The day prior to the initial evaluation, the owner administered the ivermectin solution in the morning and returned in the evening to find the dog apparently blind with mydriatic pupils. The dose administered to dog 2 immediately prior to the development of clinical toxic signs was the last of the solution in the bottle.

Results of a physical examination were unremarkable with the exception of some areas of dermal crusting and alopecia on the ventrum of the neck. The dog behaved as if partially sighted in ambient room light. Pupils were equal and widely dilated. Direct and consensual PLRs were sluggish and incomplete in each eye. In both eyes, menace responses were present, dazzle reflexes were absent, and palpebral reflexes were complete. Globe positions and movements were considered normal in both eyes. The dog’s other neurologic examination findings were also apparently normal.

A complete ophthalmic examination involving slit-lamp biomicroscopy and binocular indirect ophthalmoscopy was performed. Both eyes were open and appeared comfortable. There was no overt ocular discharge or facial asymmetry. Other than some corneal ghost vessels and mild stromal fibrosis peripherally in the left eye, no abnormalities were detected in the anterior segment or vitreous humor of either eye. Both pupils were dilated with topically applied tropicamide.

Fundic examination of the left eye revealed a low-lying, targetoid bullous retinal separation (approx 1 optic disc diameter in size) located immediately medial to the optic nerve head at the tapetal-nontapetal border. There were also multiple, indistinct, linear to vermiform to circular, gray regions of suspected retinal edema or folds throughout the nontapetal fundus. Fundic examination of the dilated right eye revealed similar but more numerous regions of retinal edema and folds throughout the nontapetal fundus (Figure 2). The tapetal fundus of the right eye was apparently normal. The appearance of the optic nerve head in each eye was normal. There was no record of a previous fundic examination of dog 2. Electroretinography was performed according to the protocol used for dog 1; in dog 2, b-wave amplitude was 94 µV in the right eye and 57 µV in the left eye.

A tentative diagnosis of ivermectin toxicosis was made. A sample of serum was obtained from dog 2 and analyzed for ivermectin via LC-MS according to the protocol used for dog 1; a concentration of ivermectin greater than the method detection limit of 50 ng/g was detected, but the small sample size precluded further quantification. The dog was discharged from hospital on the day of the initial evaluation, and the owner was instructed to discontinue administration of ivermectin and observe the dog for changes in condition.

The owner reported subjective improvement in the dog’s vision over the next few days and believed that vision was normal at the time of a recheck examination 19 days after the initial evaluation. At that time, physical and neurologic examination findings were unremarkable. Complete ophthalmic examination confirmed appropriate and equal pupil size and normal direct and consensual PLRs bilaterally. The menace response and dazzle reflex in the left eye were question-able but were present in the right eye. In both eyes, palpebral reflexes were brisk and complete and globe...
position and movements were considered normal. The anterior segment and vitreous humor findings were unchanged in both eyes. A fundic examination of each eye was conducted after pupil dilation with topical application of tropicamide and revealed a normal optic nerve head, tapetum, and retinal vasculature. In both eyes, the nontapetal fundus had a symmetrically mottled appearance, which was considered within normal limits (Figure 2). There was an improvement in the ERG b-wave amplitude (160 µV in the right eye and 110 µV in the left eye). The dog was genetically tested for the multidrug sensitivity mutation (mdr1-1Δ) in the MDR1 gene and did not carry the mutation.6

Discussion

Ivermectin toxicosis in dogs is frequently reported.2-9 Clinical signs in dogs include mydriasis, blindness, hypersalivation, ataxia, signs of depression, coma, tremors, and death. Retinal lesions associated with presumed toxicosis were first described in 2 dogs in 1989.10 In that report, 1 dog had multiple retinal folds. Although that dog was unavailable for follow-up examination, the dog’s vision reportedly returned to normal. The second of those 2 dogs had multiple linear areas of dark pigmentation in the tapetal fundus and linear gray areas of edema in the nontapetal retina. Vision apparently returned in the second dog, but again, findings of a repeat fundic examination were not reported. In another report,7 a dog developed similar retinal lesions after ivermectin exposure. Although the clinical signs resolved in that dog, the fundic lesions were unchanged 2 weeks after the initial examination. Both dogs of the present report also had areas of presumptive retinal edema that were often arranged in a linear fashion and formed apparent retinal folds. Although neither dog underwent a funduscopic examination prior to the onset of blindness, the dissolution of retinal edema was coincident with the return of useful vision and restoration of normal ERG results. These findings and those described in previous reports8,9 suggest that these fold-like regions of retinal edema are characteristic of ivermectin toxicosis in dogs. A fundic examination should therefore be considered a critical part of diagnostic procedures performed in dogs that develop blindness, especially if associated with suspected ivermectin toxicosis.

To the authors’ knowledge, this is the first report of ERG findings in dogs with confirmed or suspected ivermectin toxicosis, although ERG findings in a mule foal with presumptive ivermectin toxicosis after administration of a paste containing praziquantel and ivermectin have been reported.10 It is unclear from that report10 whether a 4.5 or 22.7 mg/kg (2.1 or 10.3 mg/lb) dose of ivermectin was given. The foal was ataxic and obtunded and had mydriasis and no menace responses or PLRs in each eye. However, fundic examination findings were unremarkable and ERG b-wave amplitudes were apparently normal. On the basis of those results, the authors theorized that there was a central mechanism for the foal’s blindness. The authors also speculated that the mydriasis and PLR abnormalities were attributable to systemic toxic effects of the drug and the young age of the foal. By contrast, both dogs of this report had clinical and electrodiagnostic evidence of pathologic changes in the retinas that were likely contributory to their blindness. This difference in clinical findings may be indicative of a difference in susceptibility to ivermectin between mules and dogs or reflect different serum concentrations of the drug in the affected animals. Although both dogs of this report had notable regions of retinal edema, these comprised a small proportion of the retina and other retinal regions appeared clinically unaffected. Indeed, the clinical severity and magnitude of the retinal lesions seemed insufficient to explain the apparent blindness and mydriasis in both dogs and the extinguished ERG in dog 1. However, the improvement in ERG b-wave amplitudes in both dogs of this report that occurred in parallel with resolution of funduscopic changes and clinical signs of blindness and obtundation suggested retinal involvement in the pathogenesis of blindness. The apparent disparity between funduscopic findings and the absence of retinal function detectable via ERG in dog 1 highlights the complementary nature of these 2 test procedures. Funduscopic changes are useful in assessing the gross anatomic features of all visible aspects of the fundus including the neurosensory retina and optic nerve head. In many dogs, the sclera, choroid, tapetum, and retinal pigment epithelium are also visible. However, as with gross examination findings for any other living structures, results of funduscopic examination do not necessarily provide evidence of cellular damage unless that damage is sufficiently extensive to affect tissues grossly. Likewise, funduscopic findings do not provide evidence of retinal function, although certain inferences can be drawn when those findings are distinctly abnormal. By contrast, ERG enables assessment of the sum activity of the neurosensory retina but provides no information regarding fundic (including retinal) anatomic changes; regional retinal disease; or functional abnormalities of the optic nerve, choroid, tapetum, or sclera. This highlights the need to perform both funduscopic and ERG to gain a more comprehensive assessment of retinal structure and function in animals with visual disturbance.

Ivermectin is a mixture of 22,23-dihydro avermectin B₆ (≥ 80%) and 22,23-dihydro avermectin B₇ (≤ 20%); both are produced by the actinomycete Streptomyces avermitilis.11 Ivermectin stimulates release of the amino-acid neurotransmitter GABA from nerve endings and enhances binding of GABA to its receptor.12 Increased GABA-mediated chloride conductance blocks neuromuscular transmission in arthropods and inter-neuron-motorneuron transmission in nematodes.11 In mammals, GABA is the primary inhibitory neurotransmitter and GABA-ergic neurons are found throughout the CNS.13 However, ivermectin is effectively excluded from the CNS by a P-glycoprotein–mediated efflux mechanism that is encoded by the multidrug-resistance gene MDR1.14 Thus, the mechanism of ivermectin toxicosis in mammals with functional blood-brain and blood-retinal barriers is not known. In addition to mutation of the MDR1 gene, exposure to an excessive dose of ivermectin may considerably increase the risk of intoxication and lead to CNS depression and corresponding clinical signs via GABA activity modification. Furthermore, ivermectin is metabolized15 in the liver,
but its metabolites have not been characterized. It is possible that ivermectin metabolites, the pharmacodynamic properties of which are unknown, contribute to the clinical signs of ivermectin intoxication.

The cause of blindness in dogs with ivermectin toxicosis is not known; however, the findings in the dogs of this report suggest that both intracranial and retinal pathologic processes are involved. Theories of central blindness do not necessarily explain the prechiasmal clinical signs (mydriasis and absent PLRs) and cannot explain the presence or importance of the funduscopic lesions or the changes evident via ERG of the 2 dogs of this report. The retinal edema, folds, and suspected low-lying separations detected funduscopically during the acute phase of toxicosis in dogs of the present and previous reports suggest an inflammatory or vascular mechanism. Although eyes of the dogs of this report were not examined histologically, there was no funduscopic evidence of inflammatory cell infiltrate. Rather, the lesions had the appearance of edema, potentially representing a vascular transudate. This may have been the result of the vasodilatory effect of GABA. Although the authors are unaware of whether this effect has been identified in the retinal vasculature of dogs, it does occur in cerebral arteries of many species, including dogs. Certainly, GABAergic receptors are expressed on most cell types within the retina and GABA is considered the primary inhibitory neurotransmitter of the vertebrate retina as it is in the CNS of mammals. Therefore, if ivermectin crosses the blood-retinal barrier, it is possible that it facilitates GABA-mediated inhibition of visual output from the retina independent of any additional intracranial effects.

For the dogs of this report, analysis of serum for ivermectin was performed by use of LC-MS. This technique is highly specific and sensitive for detection of ivermectin, and it is the method of choice in medical investigations. Results of serum ivermectin analysis confirmed the suspicion that dog 1 had ingested the drug. This dog was not administered ivermectin by the owner and was not currently receiving any ivermectin-based medications. Therefore, the dose ingested was unknown. The exact nature of exposure was not determined but was presumed to be either ingestion of spilled ivermectin paste or horse feces because the dog was reported to be a scavenger by nature. To our knowledge, there are currently no data for serum ivermectin concentrations in clinical cases of toxicosis; however, there are limited data regarding plasma ivermectin concentrations in dogs given standard tablet formulations of ivermectin. In that study, oral administrations of single doses of ivermectin (6 or 100 µg/kg [2.7 or 45.5 µg/lb]) resulted in peak plasma concentrations of 2.97 or 44.3 ng/g, respectively, within 8 hours of administration. Of the 2 dogs of this report, serum ivermectin concentration in dog 1 was 1,040 ng/g at approximately 1 day following exposure, which confirmed that exposure was excessive and most likely > 100 µg/kg. On the basis of our experience, it is evident that toxicologic analysis can be used to confirm exposure to ivermectin in a dog whose exposure cannot otherwise be verified.

Previous reports of ivermectin poisonings were based on known or presumed exposure with compatible signs rather than on measured circulating concentrations.

The dose of ivermectin that was administered to dog 2 immediately prior to the development of clinical signs of toxicosis was the last of the contents of the bottle. Poor mixing may have concentrated the drug in the residual solution, resulting in a larger final dose. Alternatively, daily administration of ivermectin for 8 weeks may have resulted in drug accumulation if the dog’s ability to excrete and metabolize ivermectin was exceeded. It is also possible that ivermectin may be highly bound to albumin in dogs, as it is in people. If so, dogs with low albumin concentration may have an increased proportion of free ivermectin in circulation. Serum albumin concentration was not analyzed in dog 2.

Neither dog of the present report was a carrier of the MDRI mutation. Ivermectin susceptibility associated with a deletion mutation in the multidrug-resistance gene (MDRI) has been reported in Collies and an Australian shepherd. The mutation has also been found in 7 other dog breeds. The MDRI gene encodes P-glycoprotein, a transmembrane protein that is important in blood-brain barrier function because it acts as a drug-efflux pump. Reduced function of this protein may lead to increased susceptibility to toxic effects of drugs such as ivermectin that are P-glycoprotein substrates.

The findings in the dogs of this report suggest that a fundic examination is a critical part of initial assessment of dogs that develop blindness, especially if ivermectin toxicosis is suspected. Multifocal regions of retinal edema with or without retinal folds and separation should prompt consideration of ivermectin toxicosis. Assuming these lesions are causally related to the toxic effects of ivermectin, clinical progress of the 2 dogs of this report indicated that reversal of retinal lesions, improvement in retinal function as assessed via ERG, and clinical improvement of vision can be expected in affected dogs. It is also noteworthy that considerable illness may result from a single accidental exposure or multiple therapeutic administrations of ivermectin, even in dogs that do not have the MDRI mutation. As illustrated in the present report, LC-MS analysis of serum is an effective method for detection and quantitation of circulating ivermectin. In animals with suspected ivermectin poisoning, serum samples should be obtained at various time points beginning as early after exposure as possible. The suspected source material should also be retained for analysis. By application of the clinical and toxicologic procedures used in the dogs of this report, a diagnosis of ivermectin toxicosis can be rapidly determined.

a. Cardell veterinary blood pressure monitor, model 9301V, CAS Medical Systems Inc, Brandford, Conn.
b. RetinoGraphics BPM-100 System ERG/VEP, RetinoGraphics Inc, Norwalk, Conn.
c. IVERCARE (1.87% ivermectin), Farnam Co Inc, Phoenix, Ariz.
d. High pressure liquid chromatograph, model 1100, Agilent, Santa Clara, Calif.
e. C18 monolith column, Chromolith RP-18e, Merck, Darmstadt, Germany.
f. Mass spectrometer, model 4000 Qtrap, Applied Biosystems, Foster City, Calif.
g. Sigma Chemical Co, St Louis, Mo.
h. UC Davis Veterinary Genetics Laboratory, University of California, Davis, Calif.
References