Title: Diminazene aceturate neurotoxicity in a dog

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Answers:

1) Morphologic diagnosis

Brain (basal nuclei, thalamus, and cerebellar medulla), focal symmetrical hemorrhagic malacia.

2) Differential diagnoses

Diminazene aceturate toxicosis, thiamine deficiency, metronidazole toxicosis, and toxoplasmosis.

Microscopic findings: Focally extensive hemorrhage and numerous neutrophils were noted in the cerebellar medulla, thalamus, and basal nuclei (Figures 4 and 5). Additionally, there was vacuolation of the neuropil, characterizing edema (Figure 5), and areas with necrotic neurons, which were angular and displayed a degenerate or completely absent nucleus [Figure 5 (arrows)]. Within hemorrhagic areas there were also some foci of necrosis containing neutrophils and cellular debris (Figure 5). Focal infiltrates of neutrophils and occasional lymphocytes were identified in the lumen and wall of small numbers of blood vessels (Figure 6). The wall of these blood vessels had numerous fragmented nuclei and hyaline change [leucocytoclastic and fibrinoid vasculitis (Figure 6)]. Degenerate inflammatory cells, in which the nuclear basophilia faded because of nuclear swelling, surrounded blood vessels (perivascular cuffs) near the areas of hemorrhage (Figure 7).
Microscopic images:

Figure 4. Hematoxylin and eosin (H&E), 20x objective.

Figure 5. H&E, 40x objective.
Figure 6. H&E, 40x objective.

Figure 7. H&E, 40x objective.
**Discussion:** Diminazene aceturate is an antiprotozoal agent (aromatic diamidine) widely used in the treatment of babesiosis and trypanosomosis in some countries including South Africa, Nigeria, and Brazil. In Brazil it is also used to treat canine rangeliosis. In contrast, in the United States of America it is not approved by the Food and Drug Administration (FDA) for treatment in dogs. It is a drug deemed risky as it has a low therapeutic index. The dosage for dogs is 3.5 mg/kg intramuscularly once. The toxicity is cumulative and usually dose-related, and severe neurological signs can occur even at therapeutic doses as observed in this case. This case is one of three dogs that received a single intramuscular dose of diminazene aceturate (3.5 mg/kg) and died. Genetic variation or individual susceptibility (idiosyncratic reaction) may contribute to increased exposure to the brain and the toxicity observed at therapeutic doses.

Typical clinical signs of diminazene aceturate toxicosis include neurological changes, head tilt, tetraparesis, extensor stiffness, seizures, generalized muscle tremors (high frequency and low-amplitude), ataxia, and falling. The clinical course varies from 12 hours up to 7 days. The clinical signs reflect lesions in the medulla oblongata, pons, cerebellar medulla and peduncles, thalamus, midbrain, and basal nuclei. A definitive diagnosis of toxicosis in a live animal relies on history (treatment with diminazene aceturate) and clinical signs (thalamic-cortical syndrome and/or vestibular syndrome).

**References and Recommended literature:**


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