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The Use of Sarmazenil in the Treatment of a Moxidectin Intoxication in a Foal

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A 13-day-old Arabian Thoroughbred filly weighing 40 kg (88 lb) was presented to the University of Zurich Equine Clinic with a history of depression after deworming with moxidectin at a dose of 2 mg/kg (recommended dose 0.4 mg/kg body weight)[a] the day before admission. The foal was found recumbent 12 hours after drug administration and was in an unconscious state 6 hours later.

On admission, the filly was recumbent, unconscious, and unresponsive to stimulation. Palpebral reflexes were absent. A pulse could be detected over neither the facial nor the lateral plantar artery. The foal presented with a heart rate of 40 beats/min, a respiratory rate of 28 breaths/min, a capillary refill time of 3 seconds, and a rectal temperature of less than 89.6°F (32°C; could not be measured with standard thermometer). The distal limbs were cold to the touch. Urine drained passively from the bladder.

Venous blood gas analysis revealed a P_{O_2} of 25.7 mm Hg. No abnormalities were detected for pH (7.37; reference range 7.37–7.39), HCO_3^- (30.2 mM; reference range 27–35 mM), base excess in the blood (1.3 mM; reference range 0–6 mM), and P_{CO_2} (49.7 mm Hg; reference range 49–57 mm Hg). pH, P_{CO_2}, and P_{O_2} were temperature corrected to 86°F (30°C). With the exception of blood glucose (5.1 mM; reference range 8.2–12.3 mM), CBC results and blood biochemical results (PCV, hemoglobin, MCH, MCHC, MCV, white blood cells, platelets, total plasma protein concentration, fibrinogen, plasma sodium, potassium, chloride, magnesium, and phosphate) were within reference ranges. A blood sample was subjected to bacterial culture and tested negative.

Initially, the foal was treated with 4 mL/kg/h warmed 10% glucose solution[b] and 4 mL/kg/h lactated Ringer's solution[c] and fed with mare's milk via a nasogastric tube. The foal was kept under a heat lamp and a forced–warm air heating blanket[d] to increase her body temperature. Electrolytes were monitored and intravenously substituted accordingly. The total plasma protein concentration decreased progressively from 50 g/L to 39 g/L (reference range 48–67 g/L) during the 1st 12 hours. Therefore, the foal received 750 mL of fresh frozen plasma, stabilizing the total plasma protein concentration.

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Depending on the arterial blood gas values, supplemental oxygen was supplied via nasal insufflation (6 L/min). Ranitidine[e] (6.6 mg/kg PO q12h) was administered to prevent gastric ulcers. Broad-spectrum antimicrobial treatment with ceftiofur[f] (2 mg/kg IM q24h) was added to the therapeutic regimen because of a marked increase in the white blood cell count during the 1st day after admission to the clinic.

The foal was closely monitored, and physical examination findings were recorded every hour. Fifteen hours after admission to the clinic, the circulatory functions were stabilized and the rectal temperature was within normal limits, but the foal was still recumbent and unconscious. However, she exhibited a weak palpebral reflex and involuntary tremors of the front legs. To antagonize the effect of moxidectin, sarmazenil[g] (0.04 mg/kg IV q2h) was administered for 10 hours beginning at 14 hours postadmission. The condition of the foal improved rapidly with the administration of sarmazenil. After the 3rd injection, she started to hold her head up for periods of several seconds and progressed to a 1st attempt to stand 3 hours after the 5th sarmazenil administration. After another 4 hours, the foal stood for a period of 10 minutes. She suckled the mare several times in the hours that followed, and the nasogastric tube was removed 36 hours after starting the sarmazenil therapy.

After 48 hours, the clinical signs had resolved completely, but on day 3, a marked increase in liver-specific enzyme activities was noted. Glutamate dehydrogenase concentration was 509 U/L (reference range 8.3–13.1 U/L), aspartate transferase concentration was 1,190 U/L (reference range 226–540 U/L), and sorbitol dehydrogenase concentration was 110 U/L (reference range 1.0–8.2 U/L). Aspartate transferase and sorbitol dehydrogenase values increased even further on day 4. The white blood cell count increased from 6.8×10^9 cells/L (reference range $5.2–11.9 \times 10^9$ cells/L) on the day of admission to 19.1×10^9 cells/L on day 3. Hereafter, the leucocytosis started to resolve. On day 5 the white blood cell count returned within the normal range (6.9×10^9 cells/L), and the foal was discharged free of clinical signs and continued to progress well. Three months after discharge from the clinic, it has been reported that the foal is in good health and has shown no further signs of illness.

Moxidectin, belonging to the milbemycin group, is a widely used endectocide in several species. Similar to the avermectins, milbemycins are lipophilic, macrocyclic lactones binding to glutamate-gated chloride channels in arthropods and nematodes.[1] They have a wide safety margin in most species. Neonates have a less developed blood-brain barrier[2]; therefore, they might be more sensitive to toxicosis induced by these drugs. Moxidectin intoxications have been reported in foals as a sequel of severe drug overdosing.[3] Once moxidectin has been administered, it takes

less than 9 hours until maximum plasma concentrations in the horse are reached.[4] The foal in this report developed signs of toxicosis within 12 hours of the drug's administration.

In mammals, the lipophilic milbemycins are able to diffuse across the blood-brain barrier, but low drug concentrations are maintained in the central nervous system through the action of P-glycoprotein pumps.[5] In neonates, or after a large overdose of the drug, the P-glycoproteins in the blood-brain barrier might provide insufficient return transport from the central nervous system. The toxicity of milbemycins and avermectins results from a potentiation of the γ-aminobutyric acid (GABA) inhibitory neurotransmitter.[6–8] Moxidectin stimulates the synaptic secretion of this neurotransmitter and, moreover, leads to a postsynaptic enhancement of GABA binding at the receptor site, causing membrane hyperpolarization through opening of chloride channels.[9]

Sarmazenil acts as a competitive antagonist at the benzodiazepine binding site of the $GABA_A$ receptor in the central nervous system.[10,11] Therefore, it was hypothesized that sarmazenil might counteract the action of moxidectin at the GABA receptor by down-regulating chloride conductance. Sarmazenil is used in equine anesthesia to antagonize the action of benzodiazepines such as climazolam.[12,13] Previous studies indicated that conditions of loss of consciousness can be treated effectively with administration of sarmazenil.[14] Presumably, this benzodiazepine antagonist is able to block the action of endogenous benzodiazepine receptor agonists, which have been associated with increased GABA activity in various diseases.[15] Because of the short half-life of sarmazenil in the horse (1.6 h; Ludwig, Hamza, Heizmann, et al, unpublished data), a treatment interval of 2 hours was chosen to maintain an active drug level for a longer time period. In the foal of this report, sarmazenil was administered in the same dosage as is used to antagonize the action of climazolam in equine anesthesia.[12] Treatments were given consecutively until the foal was responsive to stimulation and tried to get up of her own accord.

The administration of sarmazenil in the presented foal was associated with a rapid regression of clinical signs without the occurrence of adverse effects. Although sarmazenil has not been described in the treatment of avermectin or milbemycin intoxications before, it is possible that the course of disease might have been similar without its application. Johnson et al[3] described the course of moxidectin overdoses in 2 foals that were treated successfully with the use of supportive therapy only. The recovery of those foals was similar to the recovery we observed in the foal presented here, treated additionally with sarmazenil. In 1 foal, the clinical course was complicated by a bladder rupture, such that the foal showed signs of recovery only 36–48 hours after admission. The 2nd foal in the report of Johnson et al[3] recovered gradually from the unconscious state 18–24 hours after admission. Although these previous reports cannot be compared directly with the foal of this report because of differences in age, time of admission, and clinical findings, the rapid reaction of the presented foal only 6 hours after the initial sarmazenil application suggests that this benzodiazepine antagonist could be of value for the treatment of a milbemycin overdose. However, further studies are necessary to confirm this possible effect of sarmazenil in antagonizing the action of macrocyclic lactones.

Footnotes

[a] Equest, Fort Dodge, Würselen, Germany
[b] Glucose 10% Ecoflac-Plus, Braun Medical, Sempach, Switzerland
[c] Ringer-Lactat Lösung, Fresenius Kabi, Stans, Switzerland
[d] WarmAir, Cincinnati Sub-Zero Products Inc, Mosteller, Cincinnati, OH
[e] Ranitidin-Injektor, Streuli, Uznach, Switzerland
[f] Excenel, Provet, Lyssach, Switzerland
[g] Sarmasol, Dr E. Graeub AG, Bern, Switzerland

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