

Suspected adverse reactions to oral administration of a praziquantel-pyrantel combination in captive cheetahs (*Acinonyx jubatus*)

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OBJECTIVE

To characterize adverse reactions to oral administration of a combination of praziquantel and pyrantel embonate or pyrantel pamoate, with or without oxantel embonate, in captive cheetahs (*Acinonyx jubatus*).

DESIGN

Retrospective case series and case-control study.

ANIMALS

16 captive cheetahs with signs of adverse reaction to oral administration of praziquantel and pyrantel, with or without oxantel embonate (affected group), and 27 cheetahs without such reactions (unaffected group), all from 3 independent facilities.

PROCEDURES

Medical records and postmortem findings for affected cheetahs were reviewed and compared with those of unaffected animals. Anthelmintic doses administered, age, and sex of cheetahs were compared between groups.

RESULTS

3 reactions in affected cheetahs were fatal, whereas the remainder ranged from mild to severe. Postmortem examination failed to reveal any disease processes or conditions to explain the deaths. No differences in anthelmintic dose were identified between affected and unaffected cheetahs for all facilities combined, and no correlation existed between dose and reaction severity. No association with sex was detected, but affected cheetahs were significantly younger than unaffected cheetahs. This difference was not significant after controlling for facility.

CONCLUSIONS AND CLINICAL RELEVANCE

Cheetahs were concluded to have had an adverse reaction to the praziquantel-pyrantel combination because of temporal proximity of onset of clinical signs to dose administration, similarity of signs to those reported for toxicosis in other species for these drugs, and a lack of other disease process or environmental explanatory factors. A highly cautious approach to the use of this drug combination is recommended for cheetahs. (*J Am Vet Med Assoc* 2017;251:1188–1195)

Prevention of infection with endoparasites such as helminths via routine, regular anthelmintic administration is an accepted and common veterinary practice in zoological facilities that house cheetahs (*Acinonyx jubatus*).^{1,2} However, evidence³ suggests that a diagnosis-based approach may be a more effective means of controlling endoparasites in cheetahs. The alternative, and more traditional, approach involves the routine treatment of cheetahs with an anthelmintic every 2 to 3 months, regardless of infection status. This more traditional strategy is broadly advocated by most anthelmintic manufacturers and is supported by various international veterinary health organizations, including the South African Veterinary Association and British Small Animal Veterinary Association.^{4,5}

Various drugs, or combinations thereof, are used as anthelmintics in cheetahs. These drugs are produced commercially for use in domestic animals such as cats and dogs but are used off-label in a variety of nondomestic species,⁶ including cheetahs.⁷ In

cats and dogs, most of these drugs reportedly have high safety margins (maximum dose before clinical signs of adverse effects are observed) and are well tolerated, with minimal adverse effects. For example, praziquantel is a common anticestodal drug used in cats and dogs for which adverse effects following oral administration are uncommon.^{8,9} The reported safety margin for oral praziquantel administration is up to 40 times the recommended dose in dogs and up to 10 times the recommended dose in cats.^{8,9} Typically used in combination with praziquantel, pyrantel (for which pamoate or embonate salt is used as a carrier) has a slightly lower but still acceptable safety margin in dogs, with up to 7 times the recommended dose tolerated with no adverse effects.^{8,10} Long-term (3-month) daily pyrantel administration at 50 mg/kg (22.7 mg/lb), PO, results in signs such as tachypnea, ataxia, and other toxic cholinergic effects,^{8,10} whereas no signs are observed when administered daily at 20 mg/kg (9.1 mg/lb).^{8,10}

The pamoate salt to which pyrantel is bound results in poor or slow gastrointestinal absorption of pyrantel, in contrast to pyrantel tartrate, which is much more readily absorbed in dogs.^{8,10} Poor gastrointestinal absorption of the pamoate formulation is cited as a reason for the high tolerance of pyrantel by pets and livestock alike.^{8,10} The rate and extent of absorption of pyrantel pamoate in conjunction with gastrointestinal dysfunction have not been reported.

Findings of clinical studies involving cats and dogs generally support the safety statements made by drug manufacturers regarding anthelmintics marketed for domestic species. Literature reviews^{6,8,11–14} indicate that toxic effects of praziquantel use in domestic animals are uncommon, and the only contraindications are for dogs and cats < 4 or < 6 weeks of age, respectively. No local or systemic adverse reactions were detected in a clinical trial involving 146 cats to which a solution of emodepside and praziquantel or a control product containing selamectin was topically applied.¹¹ However, in a different geographic region, administration of the same emodepside-praziquantel treatment to 606 cats resulted in adverse reactions, including vomiting and hypersalivation, in 12 (2%) cats.¹¹ All of these signs were mild and of brief duration, and none required veterinary treatment. The rarity of observed reactions in this larger group suggests that the lack of reactions observed in the group of 146 cats may have been an artifact of sample size, but both sets of findings confirm that adverse effects are uncommon.

In a similar study¹² by the same investigators involving oral administration of the same drug combination to 239 dogs, no adverse reactions were detected, but this finding may again have been related to sample size. Findings were similar in a smaller study¹³ involving only 30 dogs and the same treatment. Oral administration of praziquantel to horses resulted in adverse reactions in only 2 of 219 (0.9%) animals, in which signs were mild to moderate colic that lasted approximately 6 hours.¹⁴

Despite the relatively widespread use of anthelmintics licensed for use in dogs and cats and in other species, such as those housed in zoological collections, only a few reports^{3,a} have been published regarding drug efficacy or safety in nondomestic species. In the authors' experience, adverse reactions to some of the anthelmintics (or anthelmintic combinations) used in zoos have occurred, with signs ranging from mild and transient gastrointestinal disturbance to moderate and even severe neurologic signs. Following an incident at a South African facility in which 7 of 12 treated cheetahs had moderate to severe neurologic reactions, including 1 fatality, after routine (ie, without clinical signs of infection) administration of praziquantel and pyrantel embonate, we realized a need for further investigation of these and similar cases. The purpose of the study reported here was to characterize adverse reactions to routine anthelmintic treatment in captive cheetahs at 3 facilities and identify risk factors for such reactions.

Materials and Methods

Animals

Case details for 16 captive cheetahs for which adverse reactions to oral anthelmintic administration were identified between 2003 and 2015 were provided from 3 independent sources: a zoological facility in South Africa (SA facility; 7 cases, including 2 sets of siblings and 2 unrelated cheetahs), a zoological facility in the United Arab Emirates (UAE facility; 6 cases, including 2 related cheetahs), and a private veterinary practice in the United Arab Emirates (UAE-PV practice; 3 cases, all of which were siblings).

The SA facility staff also provided signalment and treatment details for an additional 5 cheetahs that received identical anthelmintic doses at the same time as the reported cases, but which had no apparent reaction. Three of these unaffected cheetahs were related to 4 affected cheetahs. Medical records from this facility were restricted to a single time point. The UAE facility provided historical medical records for the 6 cheetahs that had had an adverse reaction. These records included additional anthelmintic treatment events for each of these cheetahs (prior to, and subsequent to, the event) that resulted in no apparent adverse reaction. Details of an additional 21 cheetahs that received anthelmintics at this facility over a 12-month period but that failed to have any adverse reactions were provided. The UAE-PV practice provided details of a single adverse-reaction event from 1 anonymous facility that affected 3 cheetahs, for which a practice member had served as the attending veterinarian. The UAE-PV practice records included additional details regarding the dam of the 3 affected cheetahs, which had received the same dose and drug combination on the day of the reported cases, without any adverse reaction.

Data collection

Data were extracted from the provided records regarding cheetah age at the time of the treatment event and sex; dose of administered anthelmintic at each treatment event; medical history; timing, nature, and outcome of any adverse reaction; and post-mortem findings, when applicable. Data were then categorized into groups of affected or unaffected cheetahs as well as alternative groupings according to facility (for within-facility comparisons), prior treatment with anthelmintics, age group at the time of treatment (juvenile [< 12 months of age] or adult), and drug administered.

Statistical analysis

For comparisons between affected and unaffected cheetahs, 1 anthelmintic treatment event was selected for any unaffected cheetah for which full medical histories (and data on > 1 anthelmintic treatment) were available to avoid pseudoreplication due to repeated measures. This event was selected so that it corresponded to a day on which an adverse reac-

tion was recorded for another cheetah at the same facility and was at least the second treatment event for that animal (ie, not the first treatment event).

Continuous data were first evaluated for normality of distribution by use of the Kolmogorov-Smirnov test for normality. The administered dose of anthelmintic (praziquantel, pyrantel embonate, and oxantel embonate) was compared between affected and unaffected cheetahs with the Mann-Whitney test. Pearson correlation analysis was performed to identify any association between dose and reported reaction severity (categorized as mild [no veterinary treatment], extreme [veterinary treatment required but the cheetah survived], or fatal) in the affected group. The Fisher exact test was used to compare sex distributions between affected and unaffected cheetahs, and the Mann-Whitney test was used to compare ages at the time of treatment between these groups. These comparisons were made for cheetahs in all 3 facilities and for cheetahs within each facility (UAE-PV practice excluded because of insufficient numbers). All statistical tests were performed by use of a statistical software program.^b

Results

Animals

Sixteen cheetahs with an adverse reaction to oral anthelmintic administration and 27 cheetahs without such a reaction were included in the study (**Supplementary Table S1**; available at avmajournals.avma.org/doi/suppl/10.2460/javma.251.10.1188). Clinical signs in affected cheetahs at the 3 facilities ranged from mild to severe (including 3 deaths). In all 3 facilities, the affected cheetahs had had no change in diet, husbandry, or enclosure on the day of (or days immediately prior to) the observed reactions.

Identical to unaffected cheetahs, all affected cheetahs had received a combination of praziquantel and pyrantel embonate; 9 affected cheetahs also received oxantel embonate as part of the administered product. For the 6 cheetahs at the UAE facility that had a reaction to the combination of praziquantel, pyrantel embonate, and oxantel embonate, and for which full medical histories were available, no adverse reactions were reported for the following drugs (at any dosage within manufacturer's guidelines for domestic species): fenbendazole (5 cheetahs with between 2 and 5 exposures each), ivermectin (4 cheetahs with 4 to 7 exposures each), and doramectin (2 cheetahs each treated twice).

UAE facility—The 6 affected cheetahs reported by the UAE facility had only mild signs, observed within 10 to 120 minutes after anthelmintic administration. Signs included protruding nictitating membranes, hyperreactivity to environmental stimuli, ataxia, and stiffness in the hindquarters. These 6 cheetahs fully recovered within 12 to 24 hours after anthelmintic administration. Two cheetahs received activated charcoal administered PO, and a third re-

ceived fluid therapy and antimicrobials; the remaining 3 cheetahs recovered without treatment. On at least 1 (and up to 10) previous treatment event, all 6 cheetahs had received the same drug combination without adverse effect as administered on the day of the adverse reaction event, although the brands and therefore doses of each active ingredient had differed on most occasions. Moreover, 2 of these cheetahs subsequently received the same drug combination in months following the adverse reaction event, both without adverse reaction, and a third cheetah later received praziquantel alone without any apparent adverse effects. Records for the 21 cheetahs treated at this facility on the same day as the affected cheetahs indicated no signs of adverse reaction.

SA facility—Signs of adverse reaction in the 7 affected cheetahs at the SA facility were more severe and included 1 death. Signs were first observed approximately 2 to 3 hours after administration and included ataxia, dyspnea, and protruding nictitating membranes. Approximately 5 hours after administration, the more severely affected cheetahs ($n = 5$) had neurologic signs, including seizures, tremors, pulmonary hemorrhage, reflex biting, vomiting, and pyrexia (rectal temperature, 41.2°C [106.2°F]; reference range, 37.8° to 39.9°C [100° to 103.8°F]). One cheetah (cheetah 39) died approximately 6 hours after anthelmintic administration. Treatment with sedation, ice packs, corticosteroids, oxygen, and fluid therapy was successful in the remaining severely affected cheetahs, and full recovery was achieved within 48 hours after anthelmintic administration. Moderately affected cheetahs ($n = 2$) were treated with mild sedation, corticosteroids, and oxygen for 24 hours, and a full recovery was achieved within 48 hours after anthelmintic administration. All affected cheetahs had previously received the same drug combination in a prior treatment event with no adverse reaction noted. Five concurrently treated cheetahs at this facility had no signs of adverse reaction.

A tentative diagnosis of hyperthermia due to extreme environmental temperatures had been considered by attending veterinarians at the SA facility as a cause of the observed signs. The temperature on the day of the incident was the highest recorded for the month (32°C [89.6°F] recorded at the center of town, approx 4 km from the facility¹⁵). However, all cheetahs were considered habituated to these environmental conditions, having been housed at the facility for 3 to 12 months, provided with appropriate shelter and shade, and provided free access to fresh drinking water. The adverse reactions were first observed at midday (prior to the hottest part of the day¹⁶), and the cheetahs had been exposed to these environmental temperatures or hotter (up to 35°C [95°F]) on 6 days over the previous 2 months and on an additional 7 days (up to 42°C [107.6°F]) over the subsequent 3 months, without any signs of heat stress or hyperthermia.

A necropsy^c was performed on cheetah 39, revealing deeply congested, uncollapsed lungs with myriad pete-

chial hemorrhages and mild crepitus with marked acute diffuse protein-rich pulmonary edema. Associated findings included moderate acute diffuse tissue congestion, moderate numbers of thymic petechiae, and mild acute perivascular cerebral hemorrhage. No evidence was found of any life-threatening disease process that would have been present prior to anthelmintic treatment. The postmortem report included no mention of any potentially pathogenic microorganisms or any attempt to diagnose the presence of such organisms. However, some severe subclinical lesions were identified that may have explained the more severe reaction in this cheetah versus the others, including mild inflammation in the adrenal gland and active splenic and retropharyngeal lymphoid hyperplasia. This cheetah also had surprisingly (given that it was only 8 months old) severe gastritis; severe multifocal subacute transmural lymphoplasmacytic gastritis with mild parietal cell necrosis and marked atrophy was diagnosed. Bone marrow erythropoiesis was suspected as indicating concurrent anemia, which could have exacerbated the pulmonary edema but may also have been unrelated. The final diagnosis as to the cause of death for this cheetah was acute respiratory distress syndrome.

UAE-PV practice—Two of 3 affected cases reported by the UAE-PV practice resulted in death. The dam of the 3 affected cheetahs was not observed to have had any adverse reaction to treatment despite having received anthelmintic treatment at the same time and dose. Signs first appeared in 1 affected cub (cheetah 40) approximately 4 hours after anthelmintic administration and included vomiting, tachycardia, pulmonary hemorrhage, pyrexia, and seizures. The second affected cub at this facility (cheetah 41) was found dead approximately 5 hours after anthelmintic administration, whereas the third cub (cheetah 42) developed clinical signs, including seizures, tachycardia, ataxia, and vomiting, approximately 6 hours after anthelmintic administration. Clinical signs-based treatment for seizures and hyperthermia (IV fluid administration, sedation, corticosteroids, antimicrobials, and heparin) was successful in cheetah 42, but this animal remained mildly ataxic

for 24 hours after the first observed clinical signs of reaction. All 4 cheetahs had previously been treated with the same drug combination, without reaction.

Histologic examination^d of postmortem tissue samples from cheetahs 40 and 41 revealed mild multifocal (artifactual) collapse of the lung tissue, with small areas of subpleural red cell extravasation into peripheral alveolar spaces in cheetah 40. This cheetah received a diagnosis of acute myocardial hemorrhage, mild generalized centrilobular fatty liver changes, mild lymphocytic gastritis, and mild extramedullary hematopoiesis in the spleen. In cheetah 41, findings included diffuse acute severe alveolar edema and vascular and capillary hyperemia. This cheetah received a diagnosis of acute diffuse alveolar edema of the lung, mild mucosal colonization of *Helicobacter*-like organisms in the stomach, and mild extramedullary hematopoiesis in the spleen. Pathological changes in the heart, liver, and lungs of both cheetahs were considered nonspecific and could possibly have been agonal or related to shock, whereas gastric and splenic findings were considered background lesions. There were no specific gross or histologic lesions to suggest hyperthermia, and no additional underlying disease processes were recognized that could have explained the acute simultaneous deaths in these cubs.

Comparisons between affected and unaffected cheetahs

Mean \pm SD praziquantel dose for affected cheetahs was 5.0 ± 0.6 mg/kg (2.3 ± 0.3 mg/lb), with a range of 4.5 to 5.1 mg/kg (2.0 to 2.3 mg/lb) in all but 1 situation (7.1 mg/kg [3.2 mg/lb]). Mean pyrantel dose for affected cheetahs was 33.2 ± 21.7 mg/kg (15.1 ± 9.9 mg/lb; range, 12.8 to 58.6 mg/kg [5.8 to 26.6 mg/lb]). For unaffected cheetahs, these values were 5.5 ± 2.3 mg/kg (2.5 ± 1.0 mg/lb; range, 4.2 to 17.0 mg/kg [1.9 to 7.7 mg/lb]) for praziquantel and 14.9 ± 1.6 mg/kg (6.8 ± 0.7 mg/lb; range, 11.9 to 17.9 mg/kg [5.4 to 8.1 mg/lb]) for pyrantel. There was no detectable difference between affected and unaffected cheetahs in praziquantel or pyrantel dose when all facilities were combined ($P = 0.11$ and $P = 0.08$, respectively; **Table 1**). No difference was

Table 1—Comparisons of mean (SD) anthelmintic dose and age and sex ratios for captive cheetahs at 3 international facilities between those that had (affected; $n = 16$) or did not have (unaffected; 27) an adverse reaction to anthelmintic administration.

Variable, by group	SA facility (n = 12)	P value for SA facility only	UAE facility (n = 27)	P value for UAE facility only	UAE private practice (n = 4)	P value for all 3 facilities combined
Praziquantel dose (mg/kg)						
Affected	4.95 (0.14)	0.27	5.08 (1.03)	0.24	5.0 (0)	0.11
Unaffected	7.41 (5.36)	—	5.06 (0.45)	—	5.0 (0)	—
Pyrantel dose (mg/kg)						
Affected	56.87 (1.57)	0.003	14.98 (2.71)	0.76	14.30 (0)	0.08
Unaffected	17.06 (0.24)	—	14.44 (1.32)	—	14.30 (0)	—
Age (y)						
Affected	1.21 (0.59)	0.43	4.16 (2.81)	0.84	0.41 (0)	0.01
Unaffected	0.96 (0.48)	—	4.70 (1.89)	—	5.0 (0)	—
Male-to-female ratio						
Affected	6:1	1.00	3:3	0.52	3:0	0.20
Unaffected	3:2	—	11:10	—	0:1	—

— = Not applicable.

detected between affected and unaffected cheetahs on an individual facility basis for praziquantel at the SA ($P = 0.27$) and UAE ($P = 0.24$) facilities. Likewise, within the affected group, no correlation was identified between dose of any drug administered and reaction severity ($P = 0.52$).

The praziquantel dose administered did not differ between the SA and UAE facilities ($P = 0.75$), but mean pyrantel dose was significantly ($P < 0.001$) greater at the SA facility than at the UAE facility (sample size in the UAE-PV facility was insufficient for intra- or interfacility comparisons). Furthermore, the dose of pyrantel administered to affected cheetahs at the SA facility was significantly ($P < 0.01$) greater than that administered to unaffected cheetahs. However, no detectable difference in pyrantel dose was identified between affected and unaffected cheetahs at the UAE facility ($P = 0.76$), and the dose administered to affected cheetahs at the UAE facility was numerically lower than the dose for unaffected cheetahs at the SA facility.

A greater number of males ($n = 12$) than females (4) had an adverse reaction to anthelmintic administration, whereas the sex distribution in the unaffected group was nearly equal (14 males and 13 females), but this difference was not significant ($P = 0.20$) when data were pooled for all facilities or on an individual facility basis (Table 1). Affected cheetahs were significantly ($P = 0.01$) younger at the time of adverse reaction (mean \pm SD age, 2.16 ± 0.58 years) than were concurrently treated unaffected cheetahs (4.17 ± 0.45 years). However, within each of the SA and UAE facilities, no effect of age was identified ($P = 0.43$ for the SA facility and $P = 0.84$ for the UAE facility; the test was not performed for the UAE-PV practice owing to insufficient sample).

Discussion

The 16 cheetahs with adverse reactions to the drug combination praziquantel and pyrantel (with or without oxantel embonate) in the present study shared several clinical findings. First, signs were apparent within 4 hours after anthelmintic administration, but (in surviving cheetahs) had typically resolved 24 hours after first detection, either without any treatment or with only clinical signs-based treatment. Second, signs were typically neurologic in nature, including ataxia and seizures, which progressed to pulmonary hemorrhage and respiratory distress in more severely affected cheetahs. Third, no consistent evidence of drug overdose was recorded, with most cheetahs receiving doses within the reported safety margins for each drug (the exception being pyrantel dose in affected SA cheetahs). Moreover, no difference in dose administered was detected between affected and unaffected cheetahs when all facilities were combined. Fourth, most cheetahs had previously received the drug combination without reaction, and 2 cheetahs (with only very mild, transient adverse effects) had no adverse response after they

received the same combination in the months following the initial reaction. Fifth, no underlying disease process, condition, or other cause of illness (or death) could be concluded as causing the observed reactions. Finally, both related and unrelated cheetahs were affected within each facility, and in the case of concurrent anthelmintic administration to siblings, only some siblings were affected, whereas others had no clinical signs.

The aforementioned findings suggested that oral administration of a praziquantel-pyrantel combination was most likely responsible for signs observed in cheetahs in the present study. Specific evidence to support this supposition included the fact that adverse reactions with identical or similar clinical signs have been reported for other species following administration of these drugs.⁸⁻¹⁰ In addition, all cheetahs in the present study were considered healthy prior to anthelmintic administration, and necropsy results for the 3 cheetahs that died revealed no underlying disease state that could explain the acute and simultaneous onset of signs and death. Furthermore, pharmacokinetic studies of praziquantel indicate that maximum circulating concentrations are achieved at approximately 1.5 hours after oral administration in domestic cats¹⁷ and between 30 minutes and 4 hours after oral administration in other species, including dogs, rats, and humans.^{6,18} Similarly, maximum concentrations of pyrantel in domestic cats⁶ are reached by approximately 2 hours after oral administration. Hence, this pharmacokinetic parameter for both drugs is within the same timeframe wherein signs first appeared in all affected cheetahs in the present study.

North American (Association of Zoos & Aquariums) husbandry guidelines⁷ for cheetahs indicate that praziquantel, when administered PO at 5.5 to 6.5 mg/kg (2.5 to 3.0 mg/lb), is safe and effective, but they also suggest that higher doses may be necessary when treating *Spirometra* infections. The doses of praziquantel administered to affected cheetahs in the present study were within this range (4.5 to 5.1 mg/kg) in all but 1 situation (7.1 mg/kg). However, the cheetah that received this marginally higher praziquantel dose had only mild signs of intoxication and no significant difference in dose was detected between affected and unaffected cheetahs overall. No lethal dose of praziquantel has been determined for dogs in single-drug studies^{8,9} given that doses > 200 mg/kg (90.9 mg/lb) induce vomiting. However, cats treated parenterally with 50 to 100 mg of praziquantel/kg (22.7 to 45.5 mg/lb) develop ataxia and signs of depression, whereas parenteral administration at 200 mg/kg yields fatal reactions.^{8,9} These doses are 7 to 22 times as high as the doses received by any of the affected cheetahs in the present study (4.5 to 7.1 mg/kg).

Nonetheless, signs of praziquantel toxicosis in companion animals are similar to those in the cheetahs of the present report, including weakness, vomiting, depression, and ataxia.^{8,9} Furthermore, effects in humans also include tachypnea, pyrexia, myalgia,

diarrhea, acute respiratory failure, and pleuritic pain followed by pleural effusion, hepatosplenomegaly, and ascites.^{19–21} Therefore, it appears that affected cheetahs may have had signs of praziquantel toxicosis and that this drug may have a lower safety limit in cheetahs than in other species when provided in combination with pyrantel. No single-anthelmintic studies have yet been conducted in cheetahs.

The Association of Zoos & Aquariums cheetah husbandry guidelines⁷ suggest that a pyrantel dose of 3 to 5 mg (1.4 to 2.3 mg/lb) is safe and effective in cheetahs and can be repeated on 3 consecutive days when administered alone. This is considerably lower than the pyrantel doses administered to affected cheetahs in the present study via the products containing a combination of pyrantel and praziquantel (12.8 to 58.6 mg of pyrantel/kg). Although this evidence suggested a potential overdose, the lack of difference in pyrantel dose administered to affected and unaffected cheetahs overall, combined with an apparent lack of dose-responsive level of severity within the affected cheetahs, did not definitively support a conclusion of pyrantel overdose. However, the dose administered in some of these situations was outside the safety margins reported for pyrantel in dogs (50 mg/kg).^{8,10} It is worthy to note that the tablets containing pyrantel in the anthelmintic combination, and which resulted in these higher doses of this drug, were administered to all cheetahs in accordance with the manufacturer's guidelines (for domestic species). The drug formulation for combination anthelmintic products should therefore be carefully considered prior to administration to cheetahs.

The reported LD₅₀ (dose shown to result in death in 50% of the test population) for pyrantel is > 690 mg/kg (313.6 mg/lb) when administered PO in dogs.^{8,10} None of the 3 fatalities in the present study involved a pyrantel dose near this value (ie, affected cheetahs received 12.8 to 58.6 mg/kg). However, dogs treated daily with pyrantel for 3 months at 50 mg/kg had signs of intoxication (which were not observed in dogs treated with 20 mg/kg).¹⁰ The most common signs of pyrantel toxicosis in companion animals are tachycardia, hypersalivation, diarrhea, vomiting, tremors, convulsions, excitation, and ataxia.¹⁰ In humans, adverse reactions to pyrantel include digestive perturbation, allergic skin reactions (pruritus and urticaria), dizziness and headaches, hypotonia, paresthesia, ataxia, and weakness.²¹ Eight of the 16 affected cheetahs in the present study received doses > 50 mg/kg in a single administration event, causing 3 mild, 4 severe, and 1 fatal reactions, all of which were associated with signs similar to those reported for companion animals and humans.

Although kittens treated with much greater doses of pyrantel (300 mg/kg [136.4 mg/lb]) failed to have any clinical signs or intoxication in a reported study,¹⁰ the possibility existed that the cheetah responses in the present study occurred as a result of poor tolerance of the pyrantel dose administered (ie, affected cheetahs that received < 20 mg/kg) or a toxic reaction to the high dose (ie, affected cheetahs that received

> 50 mg/kg) provided by the administered products. For cheetahs in the latter situation, extrapolation of doses typically prescribed for domestic cats to cheetahs may be inappropriate.

The neurologic signs of affected cheetahs in the present study were somewhat more closely aligned to those of pyrantel toxicosis than of praziquantel toxicosis (ie, seizures rather than weakness or paralysis). Moreover, the variable absorption of pyrantel depending on gastrointestinal integrity⁹ may provide some explanation as to the unpredictable nature of the toxic events observed (between and within individuals).

Only limited data exist regarding tolerance of the drug combinations used in the affected cheetahs of the study reported here. Reported adverse effects in domestic cats associated with oral administration of a combination of praziquantel and pyrantel include vomiting and excessive salivation, with temporary loss of appetite or loose feces.²² However, such reactions are rare in clinical studies. Nonetheless, transient ataxia is among the voluntarily reported adverse effects of this drug combination.²²

In humans, some adverse reactions to praziquantel have been considered an indirect effect of treatment, whereby sudden release of schistosomal antigens is triggered by worm death, resulting in a Jarisch-Herxheimer-like reaction.^{19,20} No evidence of parasitic infection was apparent on necropsy of the 3 cheetahs with a fatal reaction in the present study, and parasitological screening of surviving cheetahs was not available for all animals (4/6 affected cheetahs at the UAE facility were known to be positive for *Toxascaris leonina* at the time of treatment, but the remaining 2 cheetahs were not screened, and no screening data were available for the other 2 facilities). Nonetheless, the possibility existed that a similar parasite death-related reaction occurred in the 3 nonsurviving cheetahs, although such reactions would be unlikely to have simultaneously affected multiple cheetahs within a single event, as reported here for the SA facility and UAE-PV practice.

All 3 cheetahs with a fatal reaction to anthelmintic administration had signs of gastritis (n = 2) or gastric *Helicobacter* colonization (1) detected at necropsy. Damage to the gastrointestinal mucosa reportedly increases susceptibility to pyrantel toxicosis owing to increased absorption of the drug.^{8,10} Therefore, the underlying gastric lesions could have been (partly) responsible for the severity of the reaction to administered pyrantel in these 3 cheetahs.

In light of these findings, it is possible that the affected cheetahs in the present study had poor tolerance of a typical dose (ie, per recommendations for companion animals) of praziquantel, pyrantel, or both. The lack of toxic effect observed during previous and subsequent exposure of some cheetahs to these anthelmintics indicated that this tolerance was unpredictable, inconsistent, and related to an unknown factor or factors (environmental or intrinsic) present at the time of adverse reaction. The role of gastroin-

testinal integrity (which may change throughout the lifetime of an animal) in the absorption of pyrantel is a potential explanatory factor for this unpredictability.

Increased susceptibility to adverse drug reactions, including anthelmintic treatment, has been identified in cats and dogs as potentially being under genetic influence.^{23,24} Reported adverse reactions to products containing emodepside and praziquantel in genetically predisposed dogs and cats include neurologic signs such as ataxia, hypersalivation, and seizures,²⁴⁻²⁶ as were observed in the cheetahs of the present study. Although it is feasible that a similar genetic mutation existed in at least some of the affected cheetahs (particularly related siblings that were each affected), this appeared an unlikely explanation for all adverse reactions given that 14 of the 16 cheetahs had either previous exposure to this drug combination without effect or were subsequently exposed without adverse effect.

Analysis of data from all 3 facilities revealed a significant difference in the age of affected and unaffected cheetahs, whereby younger cheetahs appeared to be at greater risk of having an adverse reaction than older cheetahs. However, this finding may have been an artifact of the opportunistic nature of our subject selection strategy; comparison of groups within each facility (where genetic relatedness of cheetahs was greater than among facilities) failed to reveal an effect of age, albeit sample sizes were small. Likewise, sex was not an influencing factor. Comparison of dose-response effects was not feasible on an individual facility basis given that dose administered was consistent within each facility.

Overall, although strong evidence was obtained to suggest the adverse reactions in the cheetahs of the present study were caused by anthelmintic administration, we are unable to state conclusively that the reported clinical signs were caused by praziquantel, pyrantel, or their combination. A great number of cheetahs held in facilities across the world are likely routinely treated with either or both drugs as part of their veterinary health-care plan without any reported adverse effects. However, the temporal proximity of onset of clinical signs to administration of the anthelmintics, the similarity of observed signs to reported signs of toxicosis in other species, and the lack of other disease process or environmental factors that could explain the signs led us to conclude that these cases most likely represented adverse reactions to praziquantel, pyrantel, or both drugs. The clinical signs and potential involvement of compromised gastrointestinal integrity in the more severely affected cheetahs (that died) supported a role for pyrantel, in particular, in the reactions.

Presuming anthelmintic administration was the cause of the reactions, administration of an anticholinergic drug such as atropine⁸ at the time of the reaction may have reduced the effects of any overdose and may therefore have been lifesaving. The use of atropine as an antidote for suspected pyrantel toxicosis should be considered as part of the emergency response protocol for future cases. However, multiple factors may be involved

in the underlying mechanism of action or predisposition of affected cheetahs and so the susceptibility of an individual to adverse reaction cannot be predicted.

Although the reactions in the present study may be considered uncommon on a global scale, and were even inconsistent over time within individual cheetahs, the potential for a severe or fatal reaction in a vulnerable species such as the cheetah, which is already known to have poor reproduction rates and compromised health in captivity, warrants a highly cautious approach to the use of these drugs in this species. It would, in fact, appear prudent for cheetah caretakers to avoid entirely the use of this drug combination, particularly given that alternatives are available that do not (to our knowledge) have any known adverse effects, such as fenbendazole, ivermectin, and doramectin. Praziquantel used alone may provide safer alternative protection against cestode infections, whereas praziquantel in combination with milbemycin oxime has also been safely (and repeatedly) used in cheetahs (authors' experience). These alternative anthelmintic regimens should be investigated for efficacy and safety in this species. Moreover, a diagnosis-based anthelmintic regimen is recommended⁹ and may be a safer alternative to prophylactic treatment of cheetahs, particularly in those known or suspected to have any degree of gastrointestinal dysfunction or disease.

Footnotes

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From this month's AJVR

Clinical characteristics and muscle glycogen concentrations in warmblood horses with polysaccharide storage myopathy

Susannah S. Lewis et al

OBJECTIVE

To characterize clinical findings for polysaccharide storage myopathy (PSSM) in warmblood horses with type 1 PSSM (PSSM1; caused by mutation of the glycogen synthase 1 gene) and type 2 PSSM (PSSM2; unknown etiology).

SAMPLE

Database with 3,615 clinical muscle biopsy submissions.

PROCEDURES

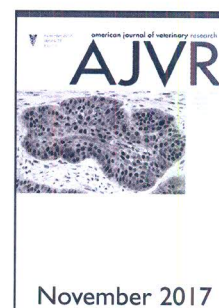
Reported clinical signs and serum creatine kinase (CK) and aspartate aminotransferase (AST) activities were retrospectively analyzed for horses with PSSM1 (16 warmblood and 430 nonwarmblood), horses with PSSM2 (188 warmblood and 646 nonwarmblood), and warmblood horses without PSSM (278). Lameness examinations were reviewed for 9 warmblood horses with PSSM2. Muscle glycogen concentrations were evaluated for horses with PSSM1 (14 warmblood and 6 nonwarmblood), warmblood horses with PSSM2 (13), and horses without PSSM (10 warmblood and 6 nonwarmblood).

RESULTS

Rhabdomyolysis was more common for horses with PSSM1 (12/16 [75%] warmblood and 223/303 [74%] nonwarmblood) and nonwarmblood horses with PSSM2 (221/436 [51%]) than for warmblood horses with PSSM2 (39/147 [27%]). Gait abnormality was more common in warmblood horses with PSSM2 (97/147 [66%]) than in warmblood horses with PSSM1 (1/16 [7%]), nonwarmblood horses with PSSM2 (176/436 [40%]), and warmblood horses without PSSM (106/200 [53%]). Activities of CK and AST were similar in warmblood horses with and without PSSM2. Muscle glycogen concentrations in warmblood and nonwarmblood horses with PSSM1 were significantly higher than concentrations in warmblood horses with PSSM2.

CONCLUSIONS AND CLINICAL RELEVANCE

Rhabdomyolysis and elevated muscle glycogen concentration were detected in horses with PSSM1 regardless of breed. Most warmblood horses with PSSM2 had stiffness and gait abnormalities with CK and AST activities and muscle glycogen concentrations within reference limits. (*Am J Vet Res* 2017;78:1305-1312)



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