

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 I**). No difference was

Table I—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.

