Abstract: A study on the impact of capture and captivity on the health of Namibian farmland cheetahs was carried out by MUNSON and MARKER-KRAUS (1997) and the Cheetah Conservation Fund. The study demonstrated that significant liver damage is incurred by cheetahs during the first week following capture, and that progressive renal damage may occur over time. The aim of this study was to find a way of reducing stress for several days in recently captured cheetahs without handling or depending on oral medication.
From the Institute for Pharmacology, Pharmacy and Toxicology of Ludwig-Maximilians University Munich¹, the Salzburg Zoo Hellbrunn (Director: Dr. R. Revers)² and the National Park Institute “Haus der Natur”, Department of Wild Biology, Salzburg³

**A POTENTIAL METHOD OF STRESS REDUCTION IN CHEETAH (ACINONYX JUBATUS) TRANSLOCATIONS USING**
**PERPHENAZINE ENANTHATE AND ZUCLOPENTHIXOL ACETATE**

By Christine Huber¹, C. Walzer² and L. Slotta Bachmayr³

**Introduction**

According to IUCN Cat Specialist Group (1996) the two largest metapopulations of free ranging cheetahs are believed to occur in East Africa (Kenya, Tanzania) and South Africa (Namibia, Botswana, Zimbabwe, Zambia). In Namibia most of the cheetahs live on private ranchland (MORSBACH, 1987), because the density of predators in the national parks and therefore competition for prey is high. The conflict between cheetah predation and farmers living from livestock farming is one of the population limiting factors. Farmers capture cheetahs in boxtraps in order to protect their livestock. According to Namibian law the farmer has the right to “remove” a cheetah from his land if it is considered to be a problem animal. The Africat Foundation collects and removes these “problem animals” from the farmland to prevent the killing of the cheetahs. The cheetahs are kept on the foundation’s facilities in approx. 30 x 30 m electric fenced enclosures until they are released back into the wild. Being wild caught animals the cheetahs have to adapt to captivity, unfamiliar environment, proximity to humans and unfamiliar food. Attempts to escape end in trauma, excoriations and superficial lacerations (MARKER-KRAUS et al., 1996).

A study on the impact of capture and captivity on the health of Namibian farmland cheetahs was carried out by MUNSON and MARKER-KRAUS (1997) and the Cheetah Conservation Fund. The study demonstrated that significant liver damage is incurred by cheetahs during the first week following capture, and that progressive renal damage may occur over time.

The aim of this study was to find a way of reducing stress for several days in recently captured cheetahs without handling or depending on oral medication.

**Pharmacology of the LAN zuclopenthixol acetate and perphenazine enanthate**

Neuroleptic drugs suppress behavioural responses without affecting spinal and other reflexes. In humans they are prescribed for their anti-psychotic effects and for the suppression of alarm situations, anxiety and psychomotoric agitation. In animals they are applied to relieve anxiety, to decrease motor activity and to moderate excitement and agitation (QUANDT and EBEDES, 1998). Long-acting tranquillizers (LAN; depot-tranquillizers) are neuroleptics which can be administered in such a form and such a manner that a single dose gives a therapeutically effective tissue concentration for at least seven days. This effect is reached by binding the esterificated tranquillizers to vegetable oils (EBEDES, 1993). Zuclopenthixol acetate belongs to the group of the thioxanthenes, whereas perphenazine enanthate is a phenothiazine-derivate. Both drugs are routinely used for capture and translocation procedures of different ungulate species in southern Africa. In the literature there is only scarce information available on the use of LAN in felids.

According to EBEDES (1993) zuclopenthixol acetate is effective within 1 hour and its sedative effect wears off at about 72 hours after injection. Perphenazine enanthate begins to be effective after 12 h, reaches its peak effect at 72 hours and decreases steadily after more than 150 hours. A combination of
zuclopenthixol acetate and perphenazine enanthate is recommended to keep the animals in a permanent stage of tranquillisation for approx. 7 days (EBEDES, 1993).

**Preliminary studies**

Zuclopenthixol acetate was used in a Namibian cheetah in a dosage of 1.0 mg/kg BW. Side effects occurred such as ataxia, acathasia, extrapyramidal reactions, protrusio membra na nictitantis, somnolence and hypothermia. Other cheetahs received 0.1-0.3 mg/kg BW and showed no or only little tranquillisation. They went off food for approx. 10 days, which was determined to be a possible side effect.

To investigate the general effect of these two neuroleptics in felidae a double blind study was carried out in 56 domestic cats. Effective dosages were established and the effect of the drugs and their combination, the duration of effect and possible side effects (inappetence) in comparison to the control group was determined. No side effects were noted in the domestic cats (HUBER, 1999, unpublished data). The established dosages were used in cheetahs in the following study.

**Material and Methods**

The study was carried out double blind. Three groups consisting of 3 cheetahs each were immobilised on day 0 using 4.0 mg/kg BW tiletamin-zolazepam (Tilest® 500, Up John), and injected deep intramuscularly with either 0.6 mg/kg BW zuclopenthixol acetate (Ciatyl-Z Acuphase®, 50 mg/ml, Bayer), 3.0 mg/kg BW perphenazine enanthate (Decatan® Depot, 100 mg/ml, Merck), or the combination of both drugs in the above mentioned dosages (Table 1). Both drugs were diluted in sterile sesame seed oil (zuclopenthixol acetate 5 mg/ml; perphenazine enanthate 10 mg/ml).

**Tab. 1: Cheetahs, Salzburg Zoo Hellbrunn**

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Zuclopenthixol acetate, mg/kg</th>
<th>Perphenazine enanthate, mg/kg</th>
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<th>BW kg</th>
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The effect of LAN in the cheetahs was evaluated using a behavioural observation protocol during their main activity time (8.00–10.00; 14.00–16.00). Starting 5 days before administration (day -5 to -1) of LAN until the effect had worn off completely. The time of observation before injection served as an individual control according to SAUDARGAS and DRUMMER (1996) small N research design (A1-B-A2-study). Scan sampling was used to record behavioural data. The behaviour was recorded using the method of instantaneous time sampling. The observation times were divided into sample intervals of 60 seconds (MARTIN and BATESON, 1993). Every 60 seconds the observed behaviour was noted in code form by the same observer. Time was measured using a stop watch (Casio 693, Alarm Chronograph®). The code system was based on an exactly defined ethogram (see appendix I). When defining activity behaviour the behavioural potential of the holding facilities had to be considered. Daily activity was statistically evaluated using ANOVA. The daily activity before injection was determined and pooled as a baseline (BL). This BL was used as control and compared with the daily activity after injection.
Results

All animals treated with one of the drugs showed a reduction in their daily activity when compared to their own BL. In all animals a sharp decrease in activity was noted on day 7, when blood samples were collected from the immobilised animals.

Fig. 1: Daily activity of the cheetahs (n=3) injected with zuclopenthixol acetate 0.6 mg/kg BW in comparison to the baseline (BL).

The animals treated with zuclopenthixol acetate showed a statistically significant (p<0.01) reduction of activity only on day one (Fig. 1). Decreased food intake, ataxia, extrapyramidal reactions, acathasia and ophtalmologic effects occurred for the first 1-2 days.

Fig. 2: Daily activity of the cheetahs (n=3) injected with perphenazine enanthate 3.0 mg/kg BW in comparison to the baseline (BL).

The calming effect of perphenazine enanthate was statistically significant (p<0.01) from day 1 until day 7. The maximum of effect was reached on day 2 (Fig. 2). No side effects were noted.
Fig. 3: Daily activity of the cheetahs (n=3) injected with zuclopenthixol acetate 0.6 mg/kg BW and perphenazine enanthate 3.0 mg/kg BW in comparison to the baseline (BL).

The cheetahs injected with the combination of both drugs showed less activity (p<0.01) from day 1 until 7 (Fig. 3). Similar side effects as in the animals injected with zuclopenthixol acetate occurred on day 1.

Discussion

In contrast to the preliminary study in domestic cats zuclopenthixol acetate alone and in combination caused side effects in the cheetahs such as inappetence, ataxia, extrapyramidal reactions, acathasia and ophtalmologic effects. The effect of zuclopenthixol acetate was statistically significant only on day 1. Perphenazine enanthate showed a different time of effect onset and duration than is mentioned in the literature in herbivore species (EBEDES, 1993). The effect onset is on day 1 and statistically significant when it reaches its maximum on day 2. The duration of the overall effect seems to be longer than 14 days. The combination of both preparations reduces daily activity more than the individual drugs alone. There might be a synergistic effect. Whereas statistic evaluation of the data gives objective information on the effect of the drugs, it may, however, on the other hand underestimate the effect.

Zuclopenthixol acetate on its own and in combination with perphenazine enanthate is not recommended for the use in cheetah because of the above mentioned side effects.

Perphenazine enanthate in a dose of 3.0 mg/kg BW produced a significant reduction of activity in captive cheetahs from day 1 until day 11 post injectionem. Lower dosages are recommended for the use in old and very young animals.

More studies on the use of LAN in different species should be carried out. As trial shows that dosages and pharmacodynamic data can not necessarily be extrapolated from trials in other species. Data has to be collected and evaluated with the most possible objectivity. Case reports and trials not using control groups and statistically evaluation of the results do not give sufficient information on the effect of LAN.

As this paper shows LAN are useful adjunct drugs in zoo and wildlife medicine and management. They could reduce stress in cheetahs being transported, translocated or during introductions to new environmental factors.
Acknowledgements
The authors want to thank: The Karl-Heinz Kurtze-Stiftung (Prof. Hasslinger) for financing the first year of the study, Dr. R. Ebert (Bayer), Dr. W. Wannenmacher (Merck) and Dr. Meyer (Up John) for supplying the drugs, Dr. T. Hännichen for lending his microscope, Dr. M. Jago, Dr. A. Hartmann, Gisi, Cilia and the staff of the Ojitwarongo Veterinary Clinic including the involved students for the helpful support in Namibia, the AfriCat Foundation, the keepers Angermann and Baskhim Kameri for their cooperation.

Summary
A potential method of stress reduction in cheetah (Acinonyx jubatus) translocations using perphenazine enanthate and zuclopenthixol acetate
Two different long-acting neuroleptics (LAN) were used to tranquilize 9 cheetahs in the Salzburg Zoo Hellbrunn. Perphenazine enanthate in a dose of 3.0 mg/kg BW and zuclopenthixol acetate at 0.6 mg/kg BW was applied to 2 groups consisting of 3 cheetahs each. A combination of both products was used in a third group of 3 animals. Effect, duration of effect and possible side effects were determined by behavioural observation using an exactly defined observation protocol. The cheetahs' behaviour was observed for comparison before, during and after the effect of the tranquillizers under the same standardised conditions. Daily activity was defined and statistically evaluated using ANOVA. A significant reduction of the activity was determined after application with all medications. Zuclopenthixol acetate alone and in combination caused inappetence, ataxia, extrapyramidal reactions, acathasia and ophthalmologic effects and is therefore not recommended for the use in cheetahs. Perphenazine enanthate did not depress appetite, caused satisfying tranquilization and showed none of the above mentioned side effects in the animals. Perphenazine enanthate seems to be a suitable and safe tranquillizer for cheetahs in the dose of 3.0 mg/kg BW. The recommended dosage should be individually adapted depending on health, age and excitement of the cheetah.

Zusammenfassung
Der Einsatz von Perphenazinenantat und Zuclopenthixolacetat als mögliche Methode zur Stressreduktion beim Umsetzen von Geparden (Acinonyx jubatus)
References


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D-52428 Jülich (Bundesrepublik Deutschland)
Appendix 1

Behavioural protocol used in the study on the cheetahs of the Salzburg Zoo Hellbrunn, activity bold-type.

1. Resting
   1.1. Lying on the side
       1.1.1. Lying on the side, head up
       1.1.2. Lying on the side, head down
   1.2. Lying in sternal position
       1.2.1. Lying in sternal position, head up
       1.2.2. Lying in sternal position, head down
   1.3. Sitting

2. Activity on the spot and locomotion
   2.1. Standing
   2.2. Walking
   2.3. Trotting
   2.4. Stalking
   2.5. Sprinting
   2.6. Climbing in tree
       2.6.1. Lying in tree
       2.6.2. Sitting in tree
       2.6.3. Standing in tree

3. Social behaviour incl. playing
   3.1. Grooming
   3.2. Jawning
   3.3. Stretching
   3.4. Rolling
   3.5. Sharpening claws
   3.6. Rubbing
   3.7. Playing

4. Metabolism - Excretion
   4.1. Urinating / Urine marking
   4.2. Defecating / Defecation marking

5. Olfactory examination
   5.1. Object sniffing

6. Metabolism - Intake
   6.1. Eating – Piece with bone
   6.2. Eating – Piece without bone
   6.3. Chewing on an old bone

7. Not visible
COMPARISON OF TWO BENZODIAZEPINE ANTAGONISTS: FLUMAZENIL AND SARMAZENIL IN THE CHEETAH (ACINONYX JUBATUS)

By C. Walzer and Christine Huber

Introduction

The largest remaining free-ranging population of cheetahs (Acinonyx jubatus) survives predominantly on farmland in Namibia (MORSBACH, 1987). Livestock predation and the subsequent anti-predator actions from the local farmers are a limiting factor in this population. Two NGO's (Cheetah Conservation Fund, Africat) carry out extensive educational programs on the one hand and on the other attempt to rehabilitate farmer-captured cheetahs. In the process of this capture-rehabilitation action the animals are routinely immobilised with a combination of tiletamine and zolazepam (Zoletil, Virbac SA, Louvain la Neuve, Belgium). The primary aim of this study was to offer a guideline for the partial antagonism of tiletamine-zolazepam anaesthesia in the field and to evaluate the possible differences between the two antagonists.

Tiletamine-zolazepam (T-Z) combinations are regularly used in veterinary medicine to anaesthetise a great number of different species (e.g. SCHOBERT, 1987; HUGUES et al., 1986; WALZER, 1995). Captive and free-ranging cheetahs are also routinely immobilised with this combination (McKENZIE and BURROUGHS, 1993; HUGUES et al., 1986). In Namibia T-Z is the drug of choice in cheetah immobilisations.

Flumazenil (Anexate "Roche" Hoffmann-LaRoche Basel, Switzerland) and sarmazenil (Sarmasol Dr. E. Graueb AG, Bern, Switzerland) are both competitive benzodiazepine receptor blockers in the CNS. Flumazenil was developed as a specific antagonist for therapeutic doses or overdoses of benzodiazepines in humans. Diazepam and midazolam induced sedation, respiratory depression and muscle relaxation in humans can be reversed by Flumazenil (GROSS et al., 1991; KLEIN and KLIDE, 1989; LAUVEN et al., 1985). Flumazenil has also been used in numerous species in veterinary anaesthesia; Dogs (HESS, 1991), cats (LIN et al., 1993), river otters (SPELMAN et al., 1997), guanacos (KARESH et al., 1998). The benzodiazepine receptor partial inverse agonist sarmazenil has been used in veterinary anaesthesia as an antagonist for clindamycin in horses (BETTSCHART-WOLFENBERGER et al., 1996), guinea-pigs (HENKE et al., 1996) and dogs (HENKE et al., 1991) for diazepam in elephant seals (WOODS et al., 1995) and squirrel monkeys (MARTIN et al., 1998). Furthermore sarmazenil is under investigation in the treatment of hepatic encephalopathy in the dog (MEYER and ROTHUIZEN, 1998).

Material and Methods

Four cheetahs were anaesthetised 3 times at an interval of 14 days with an average intramuscular dose of 4.2 ± 0.2 mg/kg BW T-Z. In the first trial no antagonist was used. In trial 2 and 3 Flumazenil at ug/kg 31 ±6 and Sarmazenil at 0.1 mg/kg respectively were applied intramuscularly 30 min after initial T-Z application. All cheetahs were held in standardised holding pens (100 m²) under standard conditions throughout the trial period. Anaesthesia was monitored using sequential rectal temperature measurements, thorax excursion and auscultation, heart rate and relative percent oxyhemoglobin saturation was measured with a pulsoximeter (Nellcor NP-20).
The following intervals were defined and observed: 1.) initial effect ataxia/sedation; 2.) lateral recumbency; 3.) first sign of recovery head held up \( t_{antag} \) time since application of the antagonist; \( t_{t-total} \) total time since application of initial T-Z; 4.) first attempt to rise (SU-A \( t_{antag} \) and SU-A \( t_{t-total} \)) and walking (SU-S \( t_{antag} \) and SU-S \( t_{t-total} \)).

Instantaneous scan sampling was used to record the behavioural data during the anaesthesia. The observation times were divided into sample intervals of 60 seconds (MARTIN and BATESON, 1993). Time was measured by a stopwatch (Casio 693 Alarm Chronograph). The results were statistically evaluated and compared using the Kruskal-Wallis test and the Mann-Whitney-U test.

**Results**

Induction of anaesthesia was rapid and calm in all 12 cases within the 3 trials. Initial effects occurred within 2.9 ± 0.8 min, lateral recumbency was achieved within 5.8 ± 3 min in all cheetahs. Myorelaxation was considered generally good.

In the trial without a partial antagonist the duration and recovery from anaesthesia was rather variable and classified as follows: head up 71 ± 28 min; first attempt to rise (SU-A) 140 ± 12 min; successful walking activity (SU-S) was 207 ± 35 min (Tab.1). The first recovery phase (approx. 35 min) was considered to be rough, as the animals would throw their heads around in a jerking-like motion repeatedly hitting the floor.

*Tab.1: Comparison of T-Z anaesthesia time intervals with T-Z-Flumazenil and T-Z-Sarmazenil. (SU-A first attempt to rise, SU-S successful rise and walk).*

<table>
<thead>
<tr>
<th>Animal Nr.</th>
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<th>Lat. Recumb.</th>
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<th>SU-A</th>
<th>SU-S</th>
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When flumazenil and sarmazenil were used as partial antagonists the duration and recovery from anaesthesia was markedly shortened: head up was achieved in 37 ± 3.5 and 36.5 ± 6.5 min in flumazenil and sarmazenil respectively (t-total). On average the head was raised 5.1 ± 1.6 min after intramuscular injection of the antagonist (t-antag) (Tab. 2). First attempts at rising were started at 74.8 ± 16.7 min and 48.3 ± 14 min with flumazenil and sarmazenil (SU-A total). Successful walking was observed at 98.8 ± 5.6 min for flumazenil and at 95.5 ± 37.6 min for sarmazenil (SU-S/total). The jerking-like motions of the head observed without an antagonist, were not noted in any of the recovery phases.

Tab. 2: Comparison of T-Z-Flumazenil and T-Z-Sarmazenil time intervals.

\[ \text{T-z-antag} = \text{time since application of antagonist} / \text{total time since T-Z application}. \]

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<th>HU (t-total)</th>
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TZ+Sarmazenil

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<th>Lat. Rec.</th>
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<th>HU (t-total)</th>
<th>SUA/t-antag</th>
<th>SUA/ total</th>
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<th>SUS/total</th>
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<td>43</td>
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<td>3</td>
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<td>3</td>
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<td>3</td>
<td>29</td>
<td>8</td>
<td>32</td>
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<tr>
<td>Mean</td>
<td>3</td>
<td>4.75</td>
<td>5.25</td>
<td>36.5</td>
<td>17</td>
<td>48.25</td>
<td>64.25</td>
<td>95.5</td>
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<tr>
<td>Standard deviation</td>
<td>0.7</td>
<td>1.9</td>
<td>1.5</td>
<td>6.5</td>
<td>8.5</td>
<td>13.9</td>
<td>32.9</td>
<td>37.6</td>
</tr>
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</table>

No significant differences between the various induction periods could be found. Furthermore no significant differences could be determined between the two antagonists in any of the defined time intervals (Mann-Whitney-U test). When comparing the duration and recovery from anaesthesia a highly significant difference could be established between T-Z with and without antagonist: Time to head up; attempt to rise and successful rise and walking (Kruskal-Wallis test p<0.05).

Discussion

Induction of anaesthesia with tiletamine-zolazepam was calm and extremely rapid in all cheetahs. This is similar to the induction periods recorded in other species with this combination (WALZER, 1995; SPELMAN et al., 1997). This further demonstrates the usefulness of this combination as an emergency drug when dealing with escaped animals in a zoo setting. Recovery from anaesthesia was prolonged when an antagonist was not used (207 ±35 min). A significant shortening of the recovery period was obtained when either flumazenil or sarmazenil was used. No significant difference could be determined between the two benzodiazepine antagonists. Resedation was not noted in any of the trials.

The average dose used for the flumazenil (31 ±6 ug/kg) in this study is 2.5 times lower than the dose used by SPELMAN et al. (1997) in river otters and 3 times lower than the dosis used by KARESH et al. (1998) in guanacos. Similar to SPELMAN et al. (1997) we found a significant shortening of the recovery phase. KARESH et al. (1998) on the other hand reports that a shortening of the recovery period following flumazenil application was not apparent. Similar to findings in the European brown bear (Ursus arctos) (WALZER, 1997) he did however note a marked increase in the depth of respiration following the flumazenil application.
Similar to other studies we recorded a significant reduction in the anaesthetic recovery time when using sarmazenil. The average dose of sarmazenil used in this study was 0.1 mg/kg. This is 2.5 times higher than the dose used in ponies to antagonise clomizolam (BETTSCHART-WOLFENSBERGER et al., 1996) but 3 times lower than the dose used in guinea pigs (HENKE et al., 1996) and 10 times lower than the dose used in the study on elephant seals (WOODS et al., 1995). Comparing these different protocols is generally difficult; in the case of the ponies the benzodiazepine antagonised was clomizolam and in the guinea pigs a combination of various antagonists (naloxone, sarmazenil and yohimbine) was used. No report in the literature could be found were sarmazenil was used to antagonise zolazepam.

When using partial antagonists care must be taken to avoid adverse excitatory effects from other components in the anaesthetic combination; in this case tiletamine. If the pharmacodynamics of T-Z is known in a species the effect of partial antagonism can be anticipated. Though when flumazenil was evaluated in the domestic cat and the dog both species recovered more rapidly, the dogs demonstrated excitatory behaviour during recovery (BEDNARSKI et al., 1989; LIN et al., 1993). This study shows that cheetahs are similar to domestic cats and river otters and that partial antagonists can be used with a T-Z anaesthesia.

The administration of flumazenil sarmazenil can be recommended 30 min after application of a T-Z combination in the cheetah. Not only is the recovery period significantly shortened but the recovery is markedly calmer. An important factor to consider is the cost of the antagonists, in the dosage used in this study flumazenil is five times the price per kg. treated. Similar to SPELMAN et al. (1997) these authors advocate caution when using a benzodiazepine antagonist with a novel species as the effect can not a priori be predicted.

Acknowledgements
The authors wish to thank Dr. Leo Slotta Bachmayr for help with the statistics and the animal keepers Mr. Joe Angermann and Mr. Baskhim Kameri for their help in this project.

Summary
Comparison of two benzodiazepine antagonists: flumazenil and sarmazenil in the cheetah (Acinonyx jubatus)
This study offers a guideline for the partial antagonism of tiletamine-zolazepam (T-Z) anaesthesia in cheetahs and evaluates the possible differences between the two benzodiazepine antagonists flumazenil and sarmazenil in this species. Four cheetahs were anaesthetised 3 times at an interval of 14 days with an average i.m. dose of 4.2 mg/kg T-Z. In trials 2 and 3 Flumazenil at 31 ug/kg and Sarmazenil at 0.1 mg/kg respectively were applied i.m. 30 min after initial T-Z application. When comparing the duration and recovery from anaesthesia a highly significant difference could be established between T-Z with and without antagonist. No significant differences could be determined between the two antagonists. The authors generally advocate caution when using benzodiazepine antagonists with a novel species.

Zusammenfassung
Vergleich zwischen zwei Benzodiazepin-Antagonisten: Flumazenil und Sarmazenil beim Geparden (Acinonyx jubatus).
Diese Studie gibt Richtlinien für die partielle Antagonisierung der Anästhesie mit Tiletamin-Zolazepam (T-Z) beim Geparden, und evaluiert zusätzlich die möglichen Unterschiede zwischen diesen zwei Antagonisten. Vier Geparden wurden jeweils dreimal im Abstand von 14 Tagen mit einer durchschnittlichen i.m. Dosis von 4.2 mg/kg T-Z narkotisiert. In Versuche 2 und 3 wurde jeweils 30 min nach der initialen T-Z Applikation, 31 ug/kg Flumazenil oder 0.1 mg/kg Sarmazenil i.m. appliziert. Ein signifikanter

References


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