

**Complication with re-sedation in Southern Ground-hornbills  
(*Bucorvus leadbeateri*) following partial reversal of two  
orally administered sedation protocols**

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| Abstract:                     | The combination of midazolam, medetomidine and azaperone (MMA) was compared with the combination of butorphanol, azaperone and medetomidine (BAM) for the sedation of Southern Ground-hornbills when administered orally in bait. The BAM combination (30 mg butorphanol, 12 mg azaperone and 12 mg medetomidine per ml of solution) at a dose of 0.14 ml/kg was the only combination that did not result in re-sedation after reversal. However, induction of sedation was long, and sedation was only deep enough for capture, handling, and minor, non-invasive procedures. The MMA combination and higher doses of the BAM combination resulted in quicker inductions although individuals showed mild to severe signs of re-sedation, starting at 4 hours after reversal and continuing for as long as 17 hours after reversal. Care should therefore be taken when administering these combinations orally to Southern Ground-hornbills as it appears that absorption, metabolism, and excretion is unpredictable in this species |

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### TITLE OF CASE

Complication with re-sedation in Southern Ground-hornbills (*Bucorvus leadbeateri*) following partial reversal of two orally administered sedation protocols

### SUMMARY

The combination of midazolam, medetomidine and azaperone (MMA) was compared with the combination of butorphanol, azaperone and medetomidine (BAM) for the sedation of Southern Ground-hornbills when administered orally in bait. The BAM combination (30 mg butorphanol, 12 mg azaperone and 12 mg medetomidine per ml of solution) at a dose of 0.14 ml/kg was the only combination that did not result in re-sedation after reversal. However, induction of sedation was long, and sedation was only deep enough for capture, handling, and minor, non-invasive procedures. The MMA combination and higher doses of the BAM combination resulted in quicker inductions although individuals showed mild to severe signs of re-sedation, starting at 4 hours after reversal and continuing for as long as 17 hours after reversal. Care should therefore be taken when administering these combinations orally to Southern Ground-hornbills as it appears that absorption, metabolism, and excretion is unpredictable in this species.

### BACKGROUND

At present, Southern Ground-hornbills (SGH) are considered globally 'Vulnerable' throughout their range in Africa by the IUCN, but within South Africa and Namibia they have been classified as 'Endangered' (1). The species is restricted to eastern and southern Africa, inhabiting suitable savanna, woodlands, and grasslands with adjoining forest patches. In South Africa, SGH have lost an estimated 70% of their range and 50% of their historic population (2,3). It is estimated that there are only about 600 family groups, and thus breeding females, left in South Africa, of which approximately one-third are safe within the protected areas of the greater Kruger National Park. They occur naturally at low densities and defend large territories (about 100 km<sup>2</sup>). Furthermore, this species is the largest bird species that breeds cooperatively and the only hornbill that is entirely faunivorous. These and other biological characteristics render them more vulnerable to extinction. In South Africa, Kemp (1987) found that the species had disappeared from parts of its former range in the northern and eastern parts of the country due to direct persecution through shooting and poisoned baits (2–6). Data from the Kruger National Park shows that, on average, only one chick is raised to adulthood every nine years. The reasons for their decline are predominantly loss of habitat to croplands, bush-encroachment, overgrazing and plantations, loss of nesting trees, primary and secondary poisoning, and electrocution.

As part of conservation efforts, SGH need to be captured in order to perform procedures such as tagging, disease testing, genetic testing, relocation and wound treatment (7–9). The process of capture is safe but is still stressful for the birds and given their advanced cognitive levels, it is extremely difficult to re-capture birds that have previously been caught (8,10). Currently, no scientifically proven protocol exists whereby SGH can be sedated or chemically immobilized for capture through oral administration of immobilising medicines (11). Oral sedation would be an alternative to darting and could therefore significantly reduce the risk of striking an air sac and injuring a bird and would allow the method to be used repeatedly on the same individuals.

According to L.V. Kemp (personal communication, November 2017), in SGH, the ideal immobilizing oral medication will produce a rapid induction, be palatable when injected into bait, be available in small injection volumes that are suitable for injection into infant mice, have a wide margin of safety, have good oral bioavailability and be at least partially if not completely reversible (i.e., provide rapid recoveries). No single immobilizing medicine currently on the veterinary market appears to comply to all these criteria and therefore a combination of 2 or more medicines is more likely to be the solution (K. Koeppel, personal communication, November 2017). A number of different medicines are currently used intravenously or intramuscularly in avian species although their application orally is yet to be fully investigated (12–20).

A group of captive SGH were housed at the National Zoological Gardens, Pretoria, South Africa. This group was used to study the efficacy of two different combinations of known wildlife sedatives, tranquilizers, and anaesthetics to immobilise these SGH when administered in bait. The selection of drugs was based on their availability in highly concentrated solution which made injection volumes practical for use in euthanised juvenile mice as bait. Doses were selected based on available data on the use of these drugs in other avian species as well as personal experience. To our knowledge, this was the first time that this species had been chemically immobilised using an oral drug protocol.

### CASE PRESENTATION

Seven SGH formed part of the avian collection of the National Zoological Gardens, Pretoria, South Africa. These birds are group-housed in purpose-built enclosures and were transferred to the facility's veterinary clinic for the purpose of the study. Transfer to the clinic was done a week before the study to allow the birds to habituate and acclimate to their new environment. Twenty-four hours prior to the study, the birds were moved from a group-enclosure at the clinic into individual enclosures and food was withheld. This was done to ensure consumption of the bait. The birds had access to water *ad lib*, and this was only be removed on the morning of the trial as a safety precaution. Euthanized juvenile mice were injected with the sedating medicine combinations and given to each of the birds. The selection of medicine combination was given to the birds at random and the birds were treated one at a time. Only the lead veterinarian was aware of treatment allocation while the remaining staff performing the monitoring were blinded as to which treatments were administered. The next bird was only given its allocated bait once the previous bird had recovered from sedation to a satisfactory level.

Three of the seven birds received a combination of medetomidine (40 mg/ml, Kyron Laboratories, Johannesburg, South Africa), midazolam (50 mg/ml, Wildlife Pharmaceuticals (Pty) Ltd., White River, South Africa) and azaperone (100 mg/ml, V-Tech Prescription Pharmacy (Pty) Ltd, Midrand, South Africa), also referred to as the MMA combination. The remaining four birds received a pre-mixed combination of 30 mg butorphanol, 12 mg azaperone and 12 mg medetomidine per ml of solution, also known as BAM (Wildlife Pharmaceuticals (Pty) Ltd., White River, South Africa). The exact doses are given in table 1 along with the details of each SGH. Dose ranges were selected to allow for flexibility depending on the effectivity of the combinations so that doses could be adjusted should a combination prove ineffective. The selection of ranges also allowed for re-dosing should animals become sedated but unmanageable. The target dose ranges were 0.12 – 0.2 ml/kg BAM and 1 – 2 mg/kg for all three components of the MMA combinations.

**Table 1** Details of the Southern Ground-hornbills and the doses of immobilizing medicines they received orally

| Bird ID | Treatment       | Gender | Age (yrs) | Weight (kg) | Medetomidine dose (mg/kg) | Azaperone dose (mg/kg) | Midazolam dose (mg/kg) | Butorphanol dose (mg/kg) |
|---------|-----------------|--------|-----------|-------------|---------------------------|------------------------|------------------------|--------------------------|
| 6       | MMA (high)      | Female | 8.8       | 3.6         | 2.0                       | 2.2                    | 2.1                    |                          |
| 4       | MMA (medium)    | Female | 7.8       | 3.6         | 1.5                       | 1.7                    | 1.5                    |                          |
| 3       | MMA (low)       | Male   | 9.9       | 4.1         | 1.2                       | 1.2                    | 1.2                    |                          |
| 7       | BAM (0.19ml/kg) | Female | 8.8       | 3.6         | 2.3                       | 2.3                    |                        | 5.8                      |

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|---|-----------------|--------|----|-----|-----|-----|-----|
| 5 | BAM (0.16ml/kg) | Male   | 12 | 4.3 | 1.9 | 1.9 | 4.8 |
| 2 | BAM (0.14ml/kg) | Female | 10 | 3.6 | 1.7 | 1.7 | 4.2 |
| 1 | BAM (0.12ml/kg) | Male   | 29 | 5.0 | 1.4 | 1.4 | 3.6 |

The MMA combination was mixed by the lead veterinarian on the day that the birds were sedated, and the dose calculated based on weights that the facility had on record for each of the birds from previous examinations. The BAM combination was pre-mixed by the manufacturer for research purposes. The BAM dose was calculated as ml/kg based on the weight of each bird.

Signs of sedation following ingestion of the bait included either head drooping, wing drooping, eyes intermittently closing, mouth opening, decreased mobility and decreased response to stimulation (figure 1).

For the MMA combination, only the medetomidine in the combination was reversed initially with administration of 5 mg atipamezole per 1 mg medetomidine. For reversal of the BAM combination, approximately 5 mg atipamezole per 1 mg medetomidine plus 1 mg naltrexone per 1 mg butorphanol was administered. All reversals were administered IM into the pectoral muscles.

The individual doses of the two drug combinations received are presented in table 1. Ingestion of the bait occurred immediately to 28 min (mean  $\pm$  standard deviation (SD) =  $7.0 \pm 10.5$  min) after the bait was given. The mean time to sedation after ingestion of the bait in the birds that received the MMA combination was  $9.3 \pm 3.1$  min whilst the mean time to sedation after ingestion in birds that received the BAM combination was  $11.5 \text{ min} \pm 5.7 \text{ min}$ . Time to handling when birds received the MMA combination was  $34.0 \pm 5.6$  min compared to birds received the BAM combination, where time to handling was  $30.5 \pm 12.4$  min. All the birds in the MMA group only reached light sedation while two of the birds in the BAM group reached moderate sedation levels, allowing for the collection of blood samples and physiological monitoring (Figure 2).

Recovery was subjectively assessed as the moment birds appeared to return to normal behaviour and had a steady gait. Recovery after administration of the reversal agent/s in the MMA group took on average  $8.3 \pm 3.2$  min compared to the BAM group, where recovery took on average only  $2.5 \pm 1.0$  min. Re-sedation was observed for the first time in SGH no. 3 at 4 hours and 13 min after administration of the reversal. The signs of re-sedation were observed as drooping wings, the head lifted, eyes closed, reduced mobility, decreased response to stimulus and an unstable gait (Figure 3). The bird was treated with 20 mg atipamezole and left undisturbed after it appeared to recover until the evening. However, it appeared sedated again when a follow-up check-up was done approximately 6 hours after the second reversal was given. An additional 20 mg atipamezole was again administered IM and the bird appeared to recover. It was left alone throughout the night but again appeared sedated the next morning, approximately 10 hours after the third reversal had been given. At this time, all the other birds in the MMA group showed signs of re-sedation ( $13.9 \pm 8.7$  hours after administration of reversal) while only 2 (birds no. 5 and 7) out of the 4 birds in the BAM group showed signs of re-sedation ( $17.4 \pm 3.1$  hours after administration of reversals).

The SGH that received the highest MMA dose also showed the most severe signs of re-sedation. This bird was found listless and unable to move and was immediately placed on oxygen supplementation and treated with 20 mg atipamezole IM. Soon after, it started responding to stimulus and was placed back in its enclosure. An hour and a half later, it still appeared sedated although it had increased mobility and was treated with 0.08 mg flumazenil IV, 1.25 mg yohimbine IM and 60 ml intravenous (IV) fluids consisting of 48 ml of ringer lactate, 4 ml of dextrose 50 % and 8 ml of voluven. Additional, flumazenil was given at a dose of 0.03 mg IV when the bird still exhibited signs of sedation an hour later. Thereafter, the bird appeared to fully recover with no further signs of sedation.

All the other birds showing signs of re-sedation the following day received 60 ml of fluids subcutaneous (SC) (consisting of 54 ml of ringer lactate and 6 ml of dextrose 50 %) and a combination of yohimbine 1.25 mg and 20 mg of atipamezole per bird except for bird no. 3 which did not receive yohimbine. Additionally, the birds in the MMA group received 0.08 mg of flumazenil to reverse the effects of midazolam.

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Following treatment with SC fluids and additional reversals, all the birds recovered and no further re-sedation was observed.

### INVESTIGATIONS

The authors previously conducted a preliminary study to elaborate on the gut transit time of different bait types in three SGH. In a randomised, cross-over design, each SGH received a juvenile mouse, a day-old chick and an adult mouse (all ethically euthanized) at least once. The bait was laced each time with coloured glitter with each bird being allocated a specific colour. Faecal samples were collected from the enclosure over a 72-hour period (or until glitter was no longer visible in the faecal samples) and the amount of glitter in each sample subjectively scored according to the amount of visible glitter present. Interestingly, samples taken at 1-2 hours after ingestion of the bait showed the highest concentration of glitter in all three bait types. All three bait types also showed a steady decrease in glitter concentration in the faecal samples over time and then a spike in glitter concentration between 18-28 hours. By 72 hours, no more glitter was visible in any of the samples. Following the results of the current study, it is hypothesized that some function of the gut in SGH may cause a spike in the break-down and absorption of feedstuff between 18-28 hours after ingestion. A repetition of this preliminary study in a larger sample size may elaborate on these findings. This spike may have contributed to the re-sedation observed in the birds since most of the re-sedations were noted after 18 hours following ingestion of the bait.

### DIFFERENTIAL DIAGNOSIS

Not applicable

### TREATMENT

When re-sedation following administration of the BAM combination occurred, treatment with 20 mg atipamezole IM, 1.25 mg yohimbine SC and 60 ml SC fluids consisting of Ringer's lactate and dextrose appeared to be effective. Re-sedation following administration of the MMA combination was successfully treated with 20 mg atipamezole IM, 0.02 mg/kg flumazenil IV and 60 ml IV/SC fluids consisting of Ringer's lactate, dextrose and voluven (IV only). Supplemental oxygen is also recommended in cases of severe re-sedation. It is recommended that treatment be repeated should re-sedation persist.

### OUTCOME AND FOLLOW-UP

Both combinations provided adequate sedation so that birds became recumbent and could be safely captured and handled. However, the level of sedation was not deep enough for painful or more invasive procedures and was inconsistent in its onset. The bird (no. 1) that received the lowest BAM dose showed signs of sedation only at 18 min after ingestion of the bait although it is likely that some of the drug combination spilled out from the bait while the bird was holding/parading with it so that it did not ingest the full dose. In comparison, the other birds that received the BAM combination showed first signs of sedation at 14 min (bird no. 2; 0.14 ml/kg dose), 5 min (bird no. 5; 0.16 ml/kg dose) and 9 min (bird no. 7; 0.19 ml/kg dose), respectively. Interestingly, the first bird to receive treatment (bird no. 1) was also the oldest bird in the group. Induction times appeared to decrease with increasing doses of BAM and only the two birds that received the two lowest doses of 0.12 ml/kg and 0.14 ml/kg BAM, did not show any signs of re-sedation. The bird that received the 0.16 ml/kg BAM dose was sedated enough for physiological monitoring and blood sampling to be done and did not show severe signs of re-sedation. It was however, treated with additional administrations of atipamezole and yohimbine approximately 19.5 hours after the initial reversal. The bird that received the highest dose of BAM (0.19 ml/kg) could also be monitored for physiological response and blood samples taken but as with the 0.16 ml/kg dose, this bird showed sign of re-sedation the next day.

None of the birds that received the MMA combination became sedated enough for physiological monitoring and all these birds exhibited signs of re-sedation. The bird that received the lowest MMA dose of 1.2 mg/kg, showed the earliest signs of re-sedation, approximately 4.25 hours after the initial reversal of sedation. The bird that received the highest MMA dose of 2 mg/kg also showed the most



severe signs of re-sedation and required numerous interventions before it finally completely recovered.

We suspect that both the medetomidine and midazolam contributed to the re-sedation observed. Medetomidine was present in both combinations and its reversal with atipamezole initially appeared to result in full recovery of the birds. When the BAM combination was used, birds appeared to re-sedate at doses of 1.95 mg/kg medetomidine and higher. This combination is therefore not advisable at doses higher than 0.14 ml/kg BAM. All the birds that received the MMA combination showed signs of re-sedation, even at medetomidine doses as low as 1.2 mg/kg, and it is therefore likely that the midazolam contributed to the re-sedation since it was not reversed. The high dose of 2.1 mg/kg midazolam caused the most severe signs of re-sedation which was likely attributable to the fact that midazolam may act as a muscle relaxant by inhibiting certain spinal pathways and directly depressing motor nerve and muscle function (21). Unlike the two birds that received the highest BAM doses, none of the birds that received the MMA combination could be safely handled before 25 minutes after ingestion of the bait. Coupled with the risk of re-sedation, the MMA combination is not advisable in this species.

### DISCUSSION

Several studies have looked at the immobilization of different avian species although very few have reported on the oral administration of neuroleptics and anaesthetics and the oral bioavailability of these drugs. In turkeys (*Meleagris gallopavo*), oral ketamine was found to be ineffective at dosages as high as 500mg/kg and it was concluded that poor oral bioavailability contributed to this (22). In the common buzzard (*Buteo buteo*), oral administration of tiletamine/zolazepam at a dose of 80mg/kg was found to be effective in enabling safe handling of the birds. However, induction was long with birds only being handled after 30-60min and effectiveness decreased if the birds received a solution, rather than a powder form, or if the laced bait was stored for 7-14 hours (23). In ring-necked parakeets (*Psittacula krameri*), oral midazolam was found to be ineffective in producing acceptable sedation whereas intranasal administration produced good results – it was thought that this was due to poor oral bioavailability as a result of first pass metabolism (24). In hispaniolan amazon parrots (*Amazona ventralis*), butorphanol was found to have high bioavailability after intramuscular injection but a bioavailability of <10% following oral administration – this precluded its use *via* this route in this species for clinical applications (17).

Alpha<sub>2</sub>-agonists such as xylazine and medetomidine are the most commonly used injectable sedatives in birds with their reversibility being a major advantage (25). Alpha<sub>2</sub>-agonists provide sufficient muscle relaxation as well as analgesia and contribute to a smooth recovery although they do produce cardiopulmonary depression which should be monitored. It is also not advised that they be used on their own for immobilization and they are generally combined with other agents (26). In SGH, they have been reportedly used in combination with ketamine although the use of ketamine is not preferred because of the slow recovery associated with dissociative anaesthetics (11). The oral bioavailability of medetomidine has not been established in avian species but good oral bioavailability has been found in cats (27). Dosages of 0.1-0.35mg/kg IM are recommended in birds (25).

Benzodiazepines such as midazolam are commonly used as pre-anaesthetic agents and for sedation in birds, but are only sedatives and do not produce anaesthesia or immobilisation when used on their own (26). Midazolam is short acting, can be administered through a variety of routes, and is preferred over the longer-acting diazepam (28). In geese (*Branta canadensis*), high doses of midazolam have been found to produce sufficient sedation to facilitate restraint for diagnostic procedures. This is particularly advantageous with dangerous birds such as large raptors (*Falconiformes spp.*), and long-legged birds such as cranes (*Gruidae spp.*) and ratites (*Ratis spp.*) (29). In other species, midazolam has good oral bioavailability (30). In general, published dosage recommendations for birds vary from 0.1 to 2 mg/kg, with lower dosages advocated for the intravenous route (28).

Butorphanol is a mixed agonist/antagonist with low activity at the mu-receptor, but strong agonist activity at the kappa-receptor. Several studies have demonstrated the efficacy of butorphanol for pain management in various avian species (17,20,26,29) and suggest that a dosage range of 1 to 4 mg/kg intramuscularly or intravenously every 1 to 2 hours may provide adequate analgesia (26,28). However, butorphanol's oral bioavailability in birds appears to be poor and in amazon parrots

butorphanol was found to have 5.8% oral bioavailability and a *per os* dose of 5mg/kg was found to have no clinical effect (17). The oral bioavailability of butorphanol in hornbill species is yet to be established.

Azaperone is a member of the butyrophenone family of tranquilizers and has a fast onset but a short duration of effect (31). It is classified as a short-acting tranquilizer, neuroleptic or antipsychotic that is primarily a dopamine receptor antagonist as well as having  $\alpha_1$ -receptor antagonistic activity. Its effect on dopamine receptors results in sedation and the potentiation of anaesthesia, while the blocking of  $\alpha_1$ -adrenergic receptors results in peripheral vasodilation (32–34). Although azaperone is not commonly used in avian species, it has been safely used at a dose of 3.3–10mg/kg IM in combination with medetomidate for the anaesthesia of ostriches (*Struthio camelus*) (35). The oral bioavailability of azaperone in birds is unknown.

### LEARNING POINTS/TAKE HOME MESSAGES

- Both protocols produced undesirable effects, manifesting as either prolonged inductions or the occurrence of re-sedations, which have major practical implications when used in either captive or wild SGH.
- The pre-mixed combination of BAM at a dose of 4.2 mg/kg butorphanol, 1.7 mg/kg azaperone, and 1.7 mg/kg medetomidine (BAM volume: 0.14 ml/kg) can be used to successfully sedate SGH although sedation is only deep enough for capture, handling, and minor, non-invasive procedures. No re-sedation was observed by the authors following administration of this dose. However, the long induction times of this protocol only make it suitable for use in captive birds.
- The long induction periods and the occurrence of re-sedation with the MMA protocol, regardless of dose, makes this combination unsuitable for use in SGH.
- When using midazolam in an oral sedation combination for SGH, it is advisable to administer flumazenil to reverse the midazolam in the combination as well as reversing the medetomidine with atipamezole.
- When using medetomidine in an oral sedation combination for SGH, cognisance should be taken of the fact that the half-life of the medetomidine is likely to exceed that of atipamezole and additional atipamezole doses should be administered if re-sedation occurs. SC administration of yohimbine is also advisable in addition to atipamezole IM.
- Sedating medicine protocols that are given orally to SGH have an unpredictable onset and duration of action. More information is required on the absorption of these drugs in the gut of this species to predict the outcome.
- In the authors opinions, both medicine combinations investigated would not be recommendable for wild SGH that may require quick sedation and complete recovery upon release back into the wild but may be suitable for healthy captive held birds where longer inductions and monitoring post-reversal are feasible.

### CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

### ETHICS STATEMENT

This study was approved by the Wildlife Pharmaceuticals Animal Ethics committee (Approval number: WPAEC-2020-GHBSEDATION-42-B) as well as by the South African National Biodiversity Institute (SANBI) National Zoological Gardens (NZG) Animal Research Ethics and Scientific Committee (Approval number: SANBI/RES/P2020/27).

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### FIGURE/VIDEO CAPTIONS

**Figure 1** First signs of sedation in a Southern Ground-hornbill (SGH) following oral administration of a combination of sedation drugs.

**Figure 2** Physiological monitoring of a Southern Ground-hornbill (SGH) sedated with a combination of butorphanol, azaperone and medetomidine (BAM) given orally

**Figure 3** Signs of re-sedation in a Southern Ground-hornbill (SGH) following reversal of medetomidine, midazolam and azaperone sedation with atipamezole.

### OWNER'S PERSPECTIVE

None

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First signs of sedation in a Southern Ground-hornbill (SGH) following oral administration of a combination of sedation drugs.

1016x862mm (72 x 72 DPI)



Physiological monitoring of a Southern Ground-hornbill (SGH) sedated with a combination of butorphanol, azaperone and medetomidine (BAM) given orally

827x832mm (72 x 72 DPI)





Signs of re-sedation in a Southern Ground-hornbill (SGH) following reversal of medetomidine, midazolam and azaperone sedation with atipamezole.

1066x1422mm (72 x 72 DPI)