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DETOMIDINE AND BUTORPHANOL FOR STANDING SEDATION IN A RANGE OF ZOO-KEPT UNGULATE SPECIES

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Abstract: General anesthesia poses risks for larger zoo species, like cardiorespiratory depression, myopathy, and hyperthermia. In ruminants, ruminal bloat and regurgitation of rumen contents with potential aspiration pneumonia are added risks. Thus, the use of sedation to perform minor procedures is justified in zoo animals. A combination of detomidine and butorphanol has been routinely used in domestic animals. This drug combination, administered by remote intramuscular injection, can also be applied for standing sedation in a range of zoo animals, allowing a number of minor procedures. The combination was successfully administered in five species of nondomesticated equids (Przewalski horse [*Equus ferus przewalskii*; $n = 1$], onager [*Equus hemionus onager*; $n = 4$], kiang [*Equus kiang*; $n = 3$], Grevy's zebra [*Equus grevyi*; $n = 4$], and Somali wild ass [*Equus africanus somaliensis*; $n = 7$]), with a mean dose range of 0.10–0.17 mg/kg detomidine and 0.07–0.13 mg/kg butorphanol; the white (*Ceratotherium simum simum*; $n = 12$) and greater one-horned rhinoceros (*Rhinoceros unicornis*; $n = 4$), with a mean dose of 0.015 mg/kg of both detomidine and butorphanol; and Asiatic elephant bulls (*Elephas maximus*; $n = 2$), with a mean dose of 0.018 mg/kg of both detomidine and butorphanol. In addition, the combination was successfully used for standing sedation in six species of artiodactylids: giraffe (*Giraffa camelopardalis reticulata*; $n = 3$), western bongo (*Tragelaphus eurycerus eurycerus*; $n = 2$), wisent (*Bison bonasus*; $n = 5$), yak (*Bos grunniens*; $n = 1$), water buffalo (*Bubalus bubalis*; $n = 4$) and Bactrian camel (*Camelus bactrianus*; $n = 5$). The mean dose range for artiodactylid species except bongo was 0.04–0.06 mg/kg detomidine and 0.03–0.06 mg/kg butorphanol. The dose in bongo, 0.15–0.20 mg/kg detomidine and 0.13–0.15 mg/kg butorphanol, was considerably higher. Times to first effect, approach, and recovery after antidote were short. The use of detomidine and butorphanol has been demonstrated to be a reliable, safe alternative to general anesthesia for a number of large ungulate species.

Key words: Artiodactyl, butorphanol, detomidine, equid, mega herbivores, standing sedation.

INTRODUCTION

Standing sedation has been used as early as the 1950s in horses.[46] In zoo medicine, however, standing sedation has been less frequently utilized because of the perceived risk of sudden arousal as described in domestic animals.[19] However, general anesthesia compromises the animal's normal physiologic function, causing cardiorespiratory depression, myopathy, and, in ruminants, regurgitation and bloat.[24] Furthermore, ultrapotent opioids like etorphine have been routinely used in both captive and free-ranging large mammals, and these drugs can have potential severe side effects.[2] Hence, because minor, noninvasive procedures are often performed in zoos, standing sedation could offer an alternative to general anesthesia.[27]

The α2-adrenergic agonists (α_2 agonists) were developed for humans in the 1960s, but because of their sedative effects they became popular in veterinary medicine.[22] Xylazine was the first α_2 agonist to be used in horses and domestic hoofstock, followed by detomidine, romifidine, medetomidine, and dexmedetomidine.[6,11–13,18,21,23,29,50]

All α_2 agonists have been demonstrated to cause cardiovascular side effects.[50] The effects vary considerably in magnitude and duration. This can be attributed to variations in the drugs' affinity for different receptor sites (α2 versus α1) and subtypes of the α_2 receptors (A, B, C, D).[20] Medetomidine is considered to be the most potent α_2 agonist, followed by detomidine, romifidine, and xylazine.[21]

Opioids are primarily analgesic drugs, but when administered alone they can produce excitation. Often they are used with α_2 agonists to enhance sedative and analgesic effects and prolong the

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period of action.[16,43] Butorphanol has minimal cardiovascular side effects and causes only moderate respiratory depression.[19] Its use has been extensively investigated in combination with α_2 agonists in domestic horses and hoofstock.[19,28,32,43,47] In particular, the combination of detomidine and butorphanol (DB) has become a popular tool in equine practice.[47]

The use of xylazine has been documented for standing procedures in yak (*Bos grunniens*), camelids, elephants, and giraffe.[1,3,8,20,31,48] An experimental α_2 agonist R5 1163 was tested as a sedative in bison (*Bison bison*), wapiti (*Cervus canadensis*), and moose (*Alces alces*).[40,44] Detomidine, romifidine, and medetomidine (as sole agents) have been sporadically used in elephant, camelids, yak, and California sea lion (*Zalopus californianus*).[17,33,42,45,48]

In analogy to domestic animals where butorphanol has been added to detomidine to enhance sedative and analgesic effects, this drug combination has also been previously used in several larger zoo species like the African elephant (*Loxodonta africana*); Grevy's (*Equus grevyi*), Hartmann's (*Equus hartmannii*), and Burchell's zebra (*Equus burchellii*); onager (*Equus hemionus onager*); Przewalski horse (*Equus ferus przewalskii*); Nile hippopotamus (*Hippopotamus amphibius*); giraffe; and greater one-horned (GOH) (*Rhinoceros unicornis*) and Sumatran rhinoceros (*Dicerorhinus sumatrensis*).[5,9,27,30,34,35,38,43,49]

The present study was aimed at expanding existing knowledge in zoo animal sedation, focusing on DB. Development of doses in new species like the kiang (*Equus kiang*), Somali wild ass (*Equus africanus somaliensis*), Southern white rhinoceros (*Ceratotherium simum simum*), Asiatic elephant (*Elephas maximus*), Western bongo (*Tragelaphus eurycerus eurycerus*), wisent (*Bison bonasus*), yak, water buffalo (*Bubalus bubalis*), and Bactrian camel (*Camelus bactrianus*) and standardization of protocols within these species and additional species like the Przewalski horse, onager, Grevy's zebra, reticulated giraffe (*Giraffa camelopardalis reticulata*), and GOH rhinoceros were the main focus of the research.

MATERIALS AND METHODS

Sedation with DB was utilized over the course of 9 yr to facilitate clinical procedures in several zoos. Data of 14 species, mentioned above, were analyzed retrospectively.

Animals were separated the evening before the procedure and were fasted overnight. On the day of the procedure, animals were locked in a stable or outside yard, whereby disturbance was kept to a minimum. The Asian elephant bulls were restrained on leg chains.

Dose rates were determined from literature, clinical records, or personal experience. The animals' body weights were estimated based on a database of weights. Detomidine (Medesedan, CP Pharma, Burgdorf, 31303, Germany) and butorphanol (Alvegesic, Alvetra, Vienna, 1090, Austria), were administered i.m. This was carried out using a CO_2-powered dart gun (Dan-inject JM Special, Wildpharm, Taunton, TA4 1YX Dorset, United Kingdom) and a plastic, compressed-air–triggered dart (Dan-inject, Wildpharm). The two drugs were mixed together, giving a total volume ranging from 3 to 10 ml and thereby dictating the size of the dart used. Asian elephants were injected i.m. with a pole syringe (Spuit Geniaplex LL 50 ml, Val d'Hony-Verdifarm N. V., Beringen, 3583, Belgium).

After i.m. injection, the degree of sedation was gauged from the animal's reaction to auditory, visual, and tactile stimuli. Time to first effect was calculated as the time from i.m. injection to the first visual signs of sedation (e.g., drooping of lower lip, salivation, ataxia). Once sedation was deemed to be sufficiently profound, animals were approached and blindfolded. The absence of tail and ear movements were considered particularly important for determining sedative depth. The time the animal was approached after i.m. injection was also recorded. If animals became recumbent after injection, this was recorded as time to recumbency. Any supplemental injections were also recorded.

Noise levels, the duration of each procedure, and the number of staff involved were all kept to a minimum. At least two human escape routes were always accessible.

Heart rate (HR) (auscultation) and respiratory rate (RR) (visualization of thoracic movements) were recorded whenever possible. Arterial blood gas and electrolyte analyses were performed in rhinoceroses using an I-STAT portable analyzer (Woodley Equipment Company Ltd., Horwich, BL6 5UE, Lancashire, United Kingdom) and an I-STAT^{CG} 8+ cartridge (Woodley Equipment Company Ltd.).

Detomidine was antagonized using atipamezole (Atipam, Eurovet Animal Health, Bladel, 5531, Noord-Brabant, The Netherlands). For complete reversal, this was administered i.v. and/or i.m. at 1.5 times the dose (in milligrams) of detomidine. Lower doses were used if only partial reversal was desired. Additionally, butorphanol was antagonized with i.v. naltrexone in rhinoceros, giraffe (2–5 mg naltrexone for each 1 mg butorphanol), and Asian elephant (1.25–5 times the dose in

Table 1. Body weight and doses (mean ± SD) of the combination detomidine and butorphanol in different wildlife species as well as a recommended total dose of DB in adult animals.[a]

	Body weight (kg) (mean ± SD)	Detomidine (mg/kg) (mean ± SD)	Butorphanol (mg/kg) (mean ± SD)	Recommended dose of DB in adults (mg)
Grevy's zebra ($n = 4$)	397 ± 8	0.10 ± 0.01	0.07 ± 0.01	40 + 30
Onager ($n = 4$)	263 ± 25	0.11 ± 0.02	0.08 ± 0.01	30 + 20
Przewalski horse ($n = 1$)	350	0.11	0.09	40 + 30
Somali wild ass ($n = 7$)	232 ± 18	0.17 ± 0.02	0.13 ± 0.03	40 + 30
Kiang ($n = 3$)	225	0.17	0.13	40 + 30
Indian rhinoceros ($n = 4$)	1,948 ± 105	0.015 ± 0.003	0.015 ± 0.003	25 + 25
White rhinoceros ($n = 12$)	1,412 ± 525	0.015 ± 0.002	0.015 ± 0.002	25 + 25
Asian elephant ($n = 2$)	4,400–5,500	0.018 ± 0.001	0.018 ± 0.001	N/A
Western bongo ($n = 2$)	150–200	0.15–0.20	0.13–0.15	30 + 20 (F); 30 + 30 (M)
Reticulated giraffe ($n = 3$)	519 ± 112	0.05 ± 0.01	0.03 ± 0.03	30 + 20–30
Yak ($n = 1$)	900	0.04	0.03	40 + 30
Wisent ($n = 5$)	600 ± 111	0.06 ± 0.01	0.04 ± 0.004	35 + 25 (F); 40 + 30 (M)
Water buffalo ($n = 4$)	538 ± 250	0.05 ± 0.01	0.04 ± 0.01	20 + 15
Bactrian camel ($n = 5$)	621 ± 125	0.06 ± 0.01	0.06 ± 0.01	35 + 35

[a] N/A = not applicable; F, female; M, male.

milligrams of butorphanol). Time to recovery (moving without ataxia, fully aware of surroundings, and normal reaction to external stimuli) after administration of the antagonist was recorded where possible. Animals were monitored until recovery was judged to be complete. Thereafter, keepers checked the animals at frequent intervals over the following 2 days.

RESULTS

The doses of DB in the different species are reported in Table 1. Times from injection to first effect, approach, and sternal recumbency (if relevant), as well as recovery time after administration of the antagonist(s), are shown in Table 2, and HRs and RRs are summarized in Table 3.

Equids

The DB protocol was used on six occasions in four Grevy's zebras for cast removal, clinical examination, and blood sampling. Different doses were administered: 40 mg detomidine and 30 mg butorphanol ($n = 3$), 35 mg detomidine and 25 mg butorphanol ($n = 2$), and 30 mg detomidine and 20

Table 2. Times to first effect, approach, and sternal after first injection of DB i.m. and time to recovery after administration of the antagonist(s) (all in minutes). The values are represented as mean ± SD unless $n \leq 3$.[a]

	No. of procedures	Time to first effect	Time to approach	Time to sternal	Time to recovery after antidote
Grevy's zebra	6	6.2 ± 1.7	18.3 ± 4.6	N/A	11.7 ± 7.6 ($n = 3$)
Onager	4	5.8 ± 1.7	14.3 ± 2.1	N/A	2 (n = 1)
Przewalski horse	2	3–4	10–21	N/A	1–2
Somali wild ass[b]	10	4.0 ± 0.3	28.7 ± 12.1	N/A	8.5 ± 4.1 ($n = 6$)
Kiang[c]	3	4–5	N/M	N/A	N/M
Indian rhinoceros	4	6.8 ± 1.5	29.3 ± 16.9	N/A	2.0 ± 0.0
White rhinoceros	14	4.9 ± 1.9	13.7 ± 4.2	11.5 ± 4.1 ($n = 4$)	3.0 ± 2.5 ($n = 6$)
Asian elephant	4	9.7 ± 2.5	N/M	N/A	4–21
Western bongo	2	5–7	13–15	N/A	N/M
Reticulated giraffe	6	5.2 ± 1.8	18.3 ± 5.7	N/A	N/M
Yak[c]	1	5	14	8	11
Wisent	5	4.2 ± 1.3	11.2 ± 4.0	N/A	5.0 ± 2.9
Water buffalo[c]	4	5.3 ± 1.7	N/M	8.3 ± 0.6 ($n = 3$)	5.0 ± 1.7 ($n = 3$)
Bactrian camel	7	6.9 ± 3.2	17.7 ± 6.9	N/A	15.0 ± 12.5 ($n = 4$)

[a] N/A = not applicable; N/M, not measured.
[b] Large Animal Immobilon was added in eight procedures.
[c] Walking sedation.

Table 3. HR and RR in different wildlife species sedated with DB i.m.[a]

	HR (beats/min)	RR (breaths/min)
Grevy's zebra ($n = 4$)	N/M	28–45 (38)
Onager ($n = 1$)	N/M	12–18
Somali wild ass ($n = 4$)	24–60 (32)	8–42 (24)
Greater one-horned rhinoceros ($n = 2$)	N/M	16–36 (24)
White rhinoceros ($n = 5$)	28–64 (44)	6–28 (14)
Western bongo ($n = 2$)	N/M	24–32 (26)
Yak ($n = 1$)	40–50 (42)	N/M
Wisent ($n = 5$)	N/M	20–36 (27)
Bactrian camel ($n = 4$)	32–42 (40)	12–48 (16)

[a] Values are represented as the range and median in parentheses. N/M indicates not measured.

mg butorphanol ($n = 1$). A supplemental dose of 10 mg detomidine and 5 mg butorphanol was given twice, once after the low and once after the median dose. All procedures were successfully performed and recoveries were uneventful after i.v. administration of atipamezole.

Five procedures were performed in four onagers. A dose of 30 mg detomidine and 20 mg butorphanol was used four times, whereas a dose of 20 mg detomidine and 20 mg butorphanol was administered once. No supplemental drugs were required. Walking sedation was achieved three times and standing sedation for minor procedures was achieved twice.[37] Atipamezole was either not administered ($n = 2$) or half ($n = 1$) or a full dose was given ($n = 2$).

A female Przewalski horse was satisfactorily sedated on two occasions for blood sampling using 40 mg detomidine and 30 mg butorphanol. Recovery was rapid (Table 2) and smooth after i.v. administration of atipamezole.

Seven Somali wild asses were sedated on 10 occasions. In the first five procedures, 35 mg detomidine and 25 mg butorphanol i.m. were used. All five animals required additional sedation with 0.2–0.3 ml Large Animal Immobilon i.m. (LAI; etorphine 2.45 mg/ml and acepromazine 10 mg/ml, Novartis Animal Health UK Ltd., Frimley, GU16 7SR, Surrey, United Kingdom). Two of these animals were then sufficiently sedated for clinical examination, but one animal had to be given naltrexone i.m. because of typical etorphine side effects (high stepping and pacing). Following LAI, two animals required additional DB (5 mg of each drug) but still could not be approached, and further attempts to achieve sedation were abandoned. The last two animals received 40 mg detomidine and 30 mg butorphanol, followed by 0.3 ml LAI. This allowed clinical examination and weighing of the animals. The three previously inadequately sedated animals were also sedated with 40 mg detomidine and 30 mg butorphanol i.m. 1 wk later. At this occasion, only one animal required an additional 0.2 ml LAI; the other two were sufficiently sedated to perform clinical examination.

LAI in Somali wild ass was administered 23 ± 10 min after initial DB injection when necessary. HR, RR (Table 3), and temperature (range: 35.1–37.1°C; median: 36.5°C) were monitored. Animals received atipamezole i.v. ($n = 6$) or i.m. ($n = 1$). If LAI had been administered, naltrexone (20 mg for each 1 mg etorphine) i.v. was administered. Recovery after i.v. administration of the antagonist(s) was rapid (Table 2). One animal that received atipamezole i.m. required 62 min to recover.

Three kiangs received 40 mg detomidine and 30 mg butorphanol i.m. for walking sedation to assist loading. No top-ups were required while the animals were successfully loaded. Sedation was partially antagonized with atipamezole i.m. Animals arrived safely at the new zoo and were unloaded uneventfully.

Rhinoceros

Four greater adult one-horned rhinoceroses (two males, two females) were sedated using 25 mg detomidine and 25 mg butorphanol. Procedures included general examination, microchip placement, blood collection, skin biopsy, and milking a lactating mother. Both females required a supplemental dose (5 mg detomidine + 5 mg butorphanol and 10 mg detomidine + 10 mg butorphanol each) before they could be approached. An arterial blood sample from the auricular artery was taken from one animal (Table 4). Recovery was uneventful after simultaneous i.v. administration of atipamezole and naltrexone.

Twelve white rhinoceroses (five males, seven females) were sedated successfully with DB on 14 occasions. Procedures included endoscopy of the upper respiratory tract, microchip placement, health checks, blood collection, reproductive assessment via rectal ultrasound, artificial insemination, and ophthalmologic examination. Accurate body weights were available for six subadult animals, and these animals received 0.015–0.017 mg/kg of both detomidine and butorphanol. Adult animals received 25 mg detomidine and 25 mg butorphanol i.m. No supplemental drugs were needed. On four occasions, animals went into sternal recumbency and remained this way

Table 4. Arterial blood gas values and biochemical parameters in 2 species of rhinoceros sedated with detomidine and butorphanol i.m. Values in white rhinoceros ($n = 5$) are expressed in mean ± SD whereas values obtained in greater one-horned rhinoceros come from one sample.[a]

	pH	$paCO_2$ mm Hg	paO_2 mm Hg	BE mmol/L	HCO_3^- mmol/L	TCO_2 mmol/L	Sat %	Na mmol/L	K mmol/L	iCa mmol/L	Glu mmol/L	PCV %	Hb g/dL
White rhinoceros	7.47 ± 0.06	44.7 ± 9.7	135.8 ± 50.6	8.6 ± 5.2	32.2 ± 5.1	33.5 ± 5.4	98.3 ± 1.7	132.3 ± 2.2	4.1 ± 0.4	1.4 ± 0.1	9.0 ± 1.4	37 ± 3	12.4 ± 1.0
Greater one-horned rhinoceros	7.50	45.6	207.1	12.4	35.5	36.9	99.8	130.0	3.3	1.2	12.7	32	10.8

[a] $paCO_2$ indicates partial arterial pressure of carbon dioxide; paO_2, partial arterial pressure of oxygen; BE, base excess; HCO_3^-, bicarbonate; TCO_2, total carbon dioxide; Sat, oxygen saturation; Na, sodium; K, potassium; iCa, ionized calcium; Glu, glucose; PCV, packed cell volume; Hb, hemoglobin.

throughout the procedures. For longer procedures, a catheter (20 ga) was placed in an auricular vein to ensure intravenous access. Arterial blood samples were taken from the ventral auricular artery in five animals (Table 4). Procedures lasted between 18 and 70 min. In two procedures lasting over an hour, small doses of ketamine (100–200 mg) were administered i.v. when the animal reacted to external stimuli. At the end of the procedure, atipamezole was administered i.v. ($n = 12$) or i.m. ($n = 2$). One of the animals that received atipamezole i.m. required a second dose i.v. because the level of sedation was still deemed to be too deep. Naltrexone (2–5 mg per mg butorphanol) was administered together with atipamezole i.v. ($n = 7$) or 10 min after atipamezole i.v. ($n = 3$). Recovery was considerably slower in animals receiving atipamezole i.m. (17 and 42 min) or naltrexone i.v. after atipamezole i.v. (9, 11, and 23 min) compared to animals receiving both antagonists i.v. together (1–7 min).

Asian elephant

An adult breeding bull (5,500 kg) had 100 mg detomidine and 100 mg butorphanol administered i.m. on three occasions. Effects of sedation included wide stand, indifference to surroundings, and dropping of the trunk. On one occasion, sedation was not deemed sufficient; hence, a supplemental injection of 50 mg detomidine and 50 mg butorphanol was administered i.v. Once sufficient sedation was achieved, ultrasonography was performed and a good quality semen sample was collected by manual rectal stimulation on all three occasions. On one occasion, 100 mg atipamezole alone was administered i.v. Recovery time was not measured but recovery was uneventful. On the other two occasions, 50 mg atipamezole and 150 mg naltrexone i.v. were administered. A second elephant bull (4,000 kg) received 80 mg detomidine and 80 mg butorphanol i.m. Both tusks were trimmed and a blood sample was taken. Forty milligrams of atipamezole and 100 mg naltrexone were administered i.v.

Artiodactylids

A female western bongo received 30 mg detomidine and 20 mg butorphanol, and 30 mg detomidine and 30 mg butorphanol was administered in a male. No supplemental drugs were required. Clinical examination included blood collection, intradermal tuberculin testing, and subcutaneous insertion of a contraceptive implant. Animals were not continuously monitored

after i.m. atipamezole administration. Recovery was sporadically checked, and both animals recovered uneventfully.

Six procedures were performed in three giraffe (two males, one female). A juvenile male needed pre-export health checks including blood collection and intradermal tuberculin testing. Detomidine was used as the sole agent on two occasions (15 and 20 mg). One year later, the same animal was successfully sedated with 30 mg detomidine and 20 mg butorphanol. Another juvenile male received 25 mg detomidine and 25 mg butorphanol for pre-export testing. An adult female was sedated twice for radiography of the lower limb (30 mg detomidine and 25 mg butorphanol and 30 mg detomidine and 30 mg butorphanol). On both occasions radiography was successful but blood collection was possible only at the higher butorphanol dose. No physiologic data were recorded during the procedures. In the first male, no antagonist was administered (no ataxia observed). In the second male, only atipamezole was administered i.m., and in the female, atipamezole and naltrexone were administered together i.m. on both occasions. After the procedures, giraffes recovered in an outdoor concrete yard. Recovery was estimated to be complete within 15–25 min after administration of the antagonist(s).

An adult male yak was sedated with 40 mg detomidine and 30 mg butorphanol for walking sedation during loading. Initially the yak went into sternal recumbency. After stimulation, the animal stood up and walked into the trailer. Movements were ataxic but balance was never lost and the yak was loaded uneventfully.[26] Atipamezole i.m. was administered after loading, and the yak had regained full consciousness within 11 min (Table 2), allowing transport to start.[26]

Five wisents (one male, four females) were sedated to allow diagnostic swabs for *Mycoplasma* identification. Pregnancy diagnosis, using rectal palpation, was also performed. Females received 35 mg detomidine and 25 butorphanol, and the male had 40 mg detomidine and 30 mg butorphanol administered. No additional doses were required. The cows received atipamezole i.v., whereas the bull received half the dose i.m. and the other half i.v. All animals recovered uneventfully after atipamezole injection (Table 2).

DB was used for walking sedation to translocate four water buffaloes. Three out of four animals went into lateral recumbency 6–8 min after injection. Open castration was performed on two recumbent males. A large adult male (900 kg) who received 40 mg detomidine and 30 mg butorphanol was partially antagonized with 10 mg atipamezole i.v., which allowed the animal to stand up 3 min after injection and walk blindfolded into a trailer. A young male (350 kg) and an adult female (400 kg) received 25 and 20 mg detomidine respectively and 15 mg butorphanol i.m. and then both received 5 mg atipamezole i.v. to stand up and walk in the container. The fourth animal (500 kg) received 20 mg detomidine and 15 mg butorphanol i.m. and walked into the container without difficulties. None of the animals received (additional) atipamezole after unloading.

DB has been used on seven occasions in four adult Bactrian camels. On five occasions 35 mg detomidine and 35 mg butorphanol were used with satisfactory results. On two occasions 30 mg detomidine and 30 mg butorphanol were administered, but a supplemental dose of 10 mg detomidine and 10 mg butorphanol was required in one of these cases. All animals remained standing. Radiography, treatment of myiasis, blood collection, and insertion of a microchip were successfully performed. All but one animal received atipamezole i.m. Time to recovery is recorded in Table 2.

DISCUSSION

Sedation with DB allowed safe procedures in (mostly) standing animals, for both handlers and animals. The data collected allowed standardization of the initial sedative doses in all species tested (Table 1).

Regarding staff safety, the authors recommend use of enclosures with at least two accessible doors to safely approach an animal from behind and to have an escape route in case of sudden arousal. A thorough briefing before the procedure is necessary to explain the possible risks of entering an enclosure with a semiconscious animal. Staff numbers in the enclosure and external stimuli should be kept to an absolute minimum so as not to unnecessarily stimulate the animal.

All equids showed signs of α_2 agonist–butorphanol sedation similar to those seen in domestic horses: indifference to the surroundings, lowering of the head, drooping of the eyelids and lower lip, and ataxia.[19] Absence of tail and ear swishing was considered to be the most reliable means to determine whether animals could be approached safely.

Dose rates administered in Grevy's zebra were lower when compared with dose rates reported in literature (Table 5). Previously, butorphanol has been administered 10 min after detomidine be-

Table 5. Reported i.m. dose rates of detomidine (D) and butorphanol (B) in several wildlife species.

	D + B (mg/kg)	Reference	Comments
Zebra	D: 0.10–0.15 + B: 0.14–0.2	27	2.45 μg/kg etorphine + 10 μg/kg acepromazine in excited animals
Grevy's zebra	D: 0.11–0.23 + B: 0.1–0.15	30	Minor surgical procedures possible
Onager	D: 0.24–0.27 + B: 0.15–0.19	30	Restraint was not possible
Przewalski horse	D: 0.12–0.27 + B: 0.06–0.12	30	Fatality in 1 case
Rhinoceros	D: 0.03 + B: 0.015	7	Sufficient for minor procedures
Indian rhinoceros	D: 0.013–0.015 + B: 0.025–0.033	5	Body weight not mentioned in manuscript (calculated on 2,000 kg)
African elephant	D: 0.129–0.197 + B: 0.121–0.197	35	Mild gastrointestinal side effects in 5 procedures

cause of the occurrence of a minor excitation when these drugs were administered together.[27] Excitation was not seen in the present study even though DB was administered together in one dart. It is likely that the excitation described previously might be a result of the higher dose of butorphanol used, as opioids are known to produce excitatory effects in horses.[14,27]

None of the zebras in the present study required incremental doses to deepen sedation, whereas, as reported previously, one-third of the study animals required additional LAI to produce adequate sedation.[27] The need for additional LAI in those study animals contributed to the nervous character of the animals during repeated procedures over a short time period.[27] Zebras in the present study were generally calm animals, but repeated procedures were also performed. Two animals had cast changes, and although the plaster saw produced considerable noise and vibration the animals remained well sedated. An earlier study, using DB with both drugs administered together, described good sedation in Grevy's zebras, allowing hoof trimming and minor surgery.[30] Hence, it is most likely that the differences in the initial dosing protocol, as mentioned above, contributed to a deeper level of sedation in the current study.

The doses used in onager and Przewalski horse in the present study were considerably lower than the one reported in the literature (Table 5). Even at the higher doses reported in literature, it was suggested that the combination would be suitable only for transport in onagers.[30] Notwithstanding, the current results show that minor procedures could also be performed. A possible explanation could be that the onagers and Przewalski horses in this study were accustomed to human contact and confined spaces and hence these animals might have been calmer before sedation, reducing the need for high doses of the DB protocol while still achieving an acceptable level of sedation.

Use of DB in Somali wild ass has not previously been reported. Based on the lead author's experience, Somali wild ass is accepted to be the most aggressive and nervous equid, followed by kiang, onager, Przewalski horse, and zebra. Therefore, higher doses than those used in other equids were necessary, as well as the option of giving incremental LAI. When the higher LAI doses (0.3 ml) were used, the animals could easily be approached but were severely head pressing, as described previously in zebras.[27] Therefore, the authors suggest limiting doses to 0.2 ml LAI or less in this species after DB sedation. A push board was used in the last two procedures, allowing animals to be cornered and blindfolded safely, whereby signs of a flight response disappeared, enabling the procedures to go ahead without the need of LAI.

To the authors' knowledge, the use of DB in kiang has also not been reported previously. In anticipation of their nervous character and with the earlier experience of the Somali wild ass procedures, it was decided to give a dose at the high end of the equid dose range.

Onset of sedation in general was faster than previously reported.[30] Approach time in the present study was similar in zebra, onager, and Przewalski horse but was much longer in Somali wild ass, presumably as a result of their nervous nature.

HR was monitored only in Somali wild ass. The anticipated typical second-degree atrioventricular blocks and bradycardia were observed.[12,19] It can only be assumed that in the other equid species similar changes might also have occurred.

Route of administration of the antagonist(s) (i.v. vs. i.m.) depended on several factors, including the nature of the individual, level of sedation

required after the procedure, and level of sedation at the end of the procedure. In general, i.v. administration was preferred in order to have immediate reversal, and no signs of excitement were seen when using this route. However, nervous equids and animals undergoing transport or benefiting from a more gradual recovery (e.g., cast changes) were reversed either i.m. or half i.m. and half i.v. Animals that were deemed to have sufficiently recovered did not receive antidotes. It was also decided not to antagonize butorphanol, in contrast to an earlier study, as this was not deemed necessary.[27]

The doses in both rhinoceros species were compared with doses reported in literature (Table 5). Two studies described higher doses, whereas a third study used a similar dose.[5,7,25] Signs of sedation were similar in both species of rhinoceros and similar to those reported in equids: animals became ataxic and unaware of their surroundings; the head and neck were lowered, almost touching the ground; the ears stopped flicking; and the eyelids and lower lip drooped.

Two female GOH rhinoceroses needed an incremental DB dose before approach. One female reacted on impact of the dart by charging towards the fence. The other female was separated from its neonate calf before sedation, causing a degree of distress.[41] It is very well known that stress and the associated release of the aspecific α_2–α_1 agonists epinephrine and norepinephrine reduces efficacy of α_2-agonistic drugs by blocking α adrenoreceptors, and therefore it is important to consider the nature of the individual animals in determining the detomidine dose.[36] The addition of small doses of ketamine (100–200 mg i.v.) seemed to deepen the level of standing sedation in the white rhinoceroses, as described previously.[25]

Of the four white rhinoceroses that went into sternal recumbency, three were male. Male rhinoceroses sedated with azaperone–butorphanol were also reported to go into sternal recumbency, whereas females remained standing.[39] This might indicate that male rhinoceroses act differently to sedative drugs, but, with only a small data set, this will need further investigation. Times to first effect in the present study were comparable to those for rhinoceroses sedated with azaperone–butorphanol.[39] The longer time to approach in the GOH rhinoceros was because of the supplemental doses needed in the nervous females, as mentioned above.

Cardiopulmonary parameters have been determined in unrestrained, unsedated white rhinoceroses (mean HR: 39 beats/min; range: 32–42 beats/min).[10] Based on these reference values, bradycardia was observed only in one animal during one measurement. This is somewhat surprising, as bradycardia is anticipated with α_2 agonists.[12,19] However, it should not be excluded that the effect of darting and afterwards the movement around the animals caused a stress reaction leading to an increased HR.

The normal mean RR in white rhinoceros was reported at 19 breaths/min (range 16–23 breaths/min).[10] Compared to these values, most white rhinoceroses in the present study were bradypneic. It has been shown that α_2 agonists cause some respiratory depression in other species and that butorphanol may slightly increase this respiratory depression.[19] The values seen were comparable to RRs seen in rhinoceroses sedated with azaperone–butorphanol (mean RR: 14.7 breaths/min; range: 9–31 breaths/min), which might indicate that, in rhinoceros, respiratory depression is mainly attributable to butorphanol.[39] Reference values for RR in conscious GOH rhinoceroses have not been reported, but it can only be assumed that they are comparable to those of white rhinoceroses. Based on these values, tachypnea was observed in two females and mainly during times of external stimuli, which might indicate that this was stress or pain related. RR in this study was higher than in GOH rhinoceroses sedated with detomidine (20–30 mg) and butorphanol (50–60 mg) (7.1 ± 2.4 breaths/min) in a different study.[5] In the latter study, the dose of butorphanol was double or more than the dose used in this study, which might explain the much lower RR due to opioid-related respiratory depression.[5]

When atipamezole was administered alone, it was observed that rhinoceroses remained moderately sedated unless naltrexone was administered. This implies that butorphanol has strong sedative effects in rhinoceros and needs to be antagonized if immediate and complete reversal of sedation is preferred.

DB in the Asiatic elephant bulls produced satisfactory sedation and animals remained standing, similar to African elephants sedated with a DB protocol (Table 5). The addition of naltrexone to antagonize butorphanol seemed to produce a quicker, more stable antagonism even with relatively low doses of atipamezole. Hence, the authors would recommend antagonizing butorphanol in this species if complete and/or rapid reversal of sedation is preferred. A total dose of the DB combination is not listed in Table 1 for

elephants as the weight differences between individual elephants are too large. However, the dose of each drug in milligrams per kilogram is very consistent in this species and can be safely used.

The present study reports the use of DB for the first time in several artiodactylid species. The dose rates across these species were comparable (Table 1) except for bongo, which needed much higher doses. Bongo in this study were extremely nervous, hence requiring an increased dose to reach satisfactory sedation.

Signs of sedation in most artiodactylid species were similar to those seen in domestic cattle and included lowering of the head and neck, drooping of the lower lip and ears, ataxia, and salivation. In camels, signs of sedation slightly differed, as instead of the head's being lowered, it was raised upwards and backwards for support against the hump.

Because giraffes can injure their handlers by kicking or swaying their neck, they were walked in a runway and were locked between two sliding doors to provide additional physical restraint. Giraffe are a high-risk species for anesthesia, and fatalities are not uncommon; hence, the development of a good sedative protocol is of major importance.[4] Furthermore, giraffe in captivity are often chronically stressed and subclinically diseased because of suboptimal dietary requirements potentially increasing the risk of anesthesia.[15] DB appears to offer a safe alternative in giraffe for different noninvasive procedures that previously required general anesthesia.

CONCLUSIONS

DB i.m. offers a safe option, for both animals and handlers, for sedation in different zoo ungulates. As demonstrated in some individuals of the species in the study, e.g., the Somali wild ass, dose rates may need to be adjusted to develop a species-specific regime, and in some there may be a need to add increments of these or other agents to facilitate safe interventions. No adverse reactions were observed for any of the animals in the study, from induction to full recovery.

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LITERATURE CITED

1. Al-Busadah KA. Effects of xylazine or xylazine followed by yohimbine on some biochemical parameters in the camel (*Camelus dromedarius*). Pak J Biol Sci. 2002;5:352–354.

2. Alford BT, Burkhart RL, Johnson WP. Etorphine and diprenorphine as immobilizing and reversing agents in captive and free-ranging mammals. J Am Vet Med Assoc. 1974;164:702–705.

3. Almubarak AI. Evaluation of intravenous administration of doxapram prior to xylazine sedation in camels (*Camelus dromedarius*). J Anim Vet Adv. 2012; 11:4455–4459.

4. Aprea F, Taylor PM, Routh A, Field D, Flach E, Bouts T. Spinal cord injury during recovery from anaesthesia in a giraffe. Vet Rec. 2011. doi: 10.1136/vr.d1685m.

5. Bapodra P, Cracknell J, Wolfe BA. Comparison of butorphanol–detomidine versus butorphanol–azaperone for the standing sedation of captive greater one-horned rhinoceroses (*Rhinoceros unicornis*). J Zoo Wildl Med. 2014;45:60–68.

6. Bettschart-Wolfensberger R, Freeman SL, Bowen IM, Aliabadi FS, Weller R, Huhtinen M, Clarke KW. Cardiopulmonary effects and pharmacokinetics of iv dexmedetomidine in ponies. Equine Vet J. 2005;37:60–64.

7. Blumer E. Restraint and anesthesia. In: AZA Rhinoceros Husbandry Resource Manual. Fort Worth (TX): Fort Worth Zoological Park; 1996. p. 46–51.

8. Bongso TA. Sedation of the Asian elephant (*Elephas maximus*) with xylazine. Vet Rec. 1979;105: 442–443.

9. Bush M. Giraffidae. In: Fowler ME, Miller RE (eds.). Zoo and Wild Animal Medicine. 5th ed. Saunders (MO): W. B. Saunders Co., Philadelphia, Pennsylvania, USA. 2003. p. 625–633.

10. Citino S, Bush M. Reference cardiopulmonary physiologic parameters for standing, unrestrained white rhinoceroses (*Ceratotherium simum*). J Zoo Wildl Med. 2007;38:375–379.

11. Clarke KW, England GCW, Goossens L. Sedative and cardiovascular effects of romifidine, alone and in combination with butorphanol, in the horse. Vet Anaesth Analg. 1991;18:25–29.

12. Clarke KW, Hall LW. "Xylazine"—a new sedative for horses and cattle. Vet Rec. 1969;85:512–517.

13. Clarke KW, Paton BS. Combined use of detomidine with opiates in the horse. Equine Vet J. 1988;20: 331–334.

14. Clutton RE. Opioid analgesia in horses. Vet Clin N Am Equine. 2010;26:493–514.

15. Colvile K, Bouts T, Hartley A, Clauss M, Routh A. Frothy bloat and serous fat atrophy in a giraffe (*Giraffa camelopardalis*) with chronic respiratory disease. In: Clauss M, Fidgett A, Hatt JM, Huisman T, Hummel J, Janssen G, Nijboer J, Plowman A (eds.). Zoo Animal Nutrition, Volume IV. Filander, Fürth (Germany): 2009. p. 219–229.

16. Cruz FS, Carregaro AB, Machado M, Antonow RR. Sedative and cardiopulmonary effects of buprenorphine and xylazine in horses. Can J Vet Res. 2011; 75:35–41.

17. Dennison S, Haulena M, Williams DC, Dawson J, Yandell BS, Gulland FMD. Determination of a sedative protocol for use in California sea lions (*Zalophus californianus*) with neurologic abnormalities undergoing electroencephalographic examination. J Zoo Wildl Med. 2008;39:542–547.

18. DeRossi R, Miglioli L, Frazílio FO, Kassab TA, Miguel GLS. Pharmacological effects of intramuscularly administration of xylazine or romifidine in calves raised on pasture . J Anim Vet Adv. 2005;4:889–893.

19. England GCW, Clarke KW. Alpha$_2$adrenoreceptor agonists in the horse—a review. Br Vet J. 1996;152: 641–657.

20. Fischer MT, Miller RE, Houston EW. Serial tranquilization of a reticulated giraffe (*Giraffa camelopardalis reticulata*) using xylazine. J Zoo Wildl Med. 1997;28:182–184.

21. Freeman SL, England GCW. Investigation of romifidine and detomidine for the clinical sedation of horses. Vet Rec. 2000;147:507–511.

22. Gozalo-Marcila M. Dexmedetomidine for balanced anaesthesia in horses. PhD Dissertation, 2013. Ghent Univ., Ghent (Belgium).

23. Greene SA. Protocols for anesthesia of cattle. Vet Clin N Am Food Anim Pract. 2003;19:679–693.

24. Harthoorn AM. Problems and hazards of chemical restraint in wild animals. Int Zoo Yearb. 1968;8: 215–220.

25. Hermes R, Göritz F, Saragusty J, Sos E, Molnar V, Reid CE, Schwarzenberger F, Hildebrandt TB. First successful artificial insemination with frozen-thawed semen in rhinoceros. Theriogenology. 2009;71:393–399.

26. Hopkins T, Dodds J, Berry K, Routh A, Strike T, Bouts T. Walking sedation with a detomidine-butorphanol combination in a yak (*Bos grunniens*). In: Proc Int Conf Zoo Wildl Dis; 2011.

27. Hoyer M, de Jong S, Verstappen F, Wolters M. Standing sedation in captive zebra (*Equus grevyi* and *Equus burchellii*). J Zoo Wildl Med. 2012;43:10–14.

28. Joubert KE, Briggs P, Gerber D, Gottschalk RG. The sedative and analgesic effects of detomidine-butorphanol and detomidine alone in donkeys. Tydskr S Afr Vet Ver. 1999;70:112–118.

29. Kamerling SG, Cravens WM, Bagwell CA. Objective assessment of detomidine-induced analgesia and sedation in the horse. Eur J Pharmacol. 1988;151:1–8.

30. Kock R, Pearce P, Taylor P. The use of detomidine and butorphanol in zoo equids. Joint Proc Am Assoc Zoo Vet Am Assoc Wildl Vet; 1988. p. 188–191.

31. Kumar A, Nigam JM, Sharma SK. Clinicobiochemical effects of xylazine in yaks. Ind J Anim Sci. 1998;68:1175–1176.

32. Lin HC, Riddell M. Preliminary study of the effects of xylazine or detomidine with or without butorphanol for standing sedation in dairy cattle. Vet Ther Res Appl Vet Med. 2003;4:285–291.

33. Marzok M, El-Khodery S. Sedative and analgesic effects of romifidine in camels (*Camelus dromedarius*). Vet Anaesth Analg. 2009;36:352–360.

34. Miller MA. Hippopotamidae. In: Fowler ME, Miller RE (eds.). Zoo and Wild Animal Medicine. 5th ed. Saunders (MO): W. B. Saunders Co., Philadelphia, Pennsylvania, USA. 2003. p. 602–612.

35. Neiffer D, Miller M, Weber M, Stetter M, Fontenot D, Robbins P, Pye G. Standing sedation in African elephants (*Loxodonta africana*) using detomidine–butorphanol combinations. J Zoo Wildl Med. 2005;36:250–2566.

36. Paddleford RR, Harvey RC. Alpha 2 agonists and antagonists. Vet Clin N Am Small Anim Pract. 1999;29:737–745.

37. Peel AJ, Bouts T, Flach E, Rivers S, Routh A. Pituitary pars intermedia dysfunction (equine Cushing's disease) in an onager (*Equus hemionus onager*). J Zoo Wildl Med. 2009;40:773–780.

38. Portas T. A review of drugs and techniques used for sedation and anaesthesia in captive rhinoceros species. Aust Vet J. 2004;82:542–549.

39. Radcliffe RW, Ferrell ST, Childs SE. Butorphanol and azaperone as a safe alternative for repeated chemical restraint in captive white rhinoceros (*Ceratotherium simum*). J Zoo Wildl Med. 2000; 31:196–200.

40. Renecker LA, Bertwistle J, Kozak HM, Hudson RJ, Chabot D, MacLean S. R51163 as a sedative for handling and transporting plains bison and wapiti. J Wildl Dis. 1992;28:236–241.

41. Routh A, Berry K, Dodds J, Bouts T. Emergency neonatal care of an Indian rhinoceros (*Rhinoceros unicornis*) calf. Proc Int Eleph Rhino Conserv Res Symp; 2011. p. 954–965.

42. Sarma B, Pathak SC, Sarma KK. Medetomidine—a novel immobilizing agent for the elephant (*Elephas maximus*). Res Vet Sci. 2002;73:315–317.

43. Schatzmann U, Armbruster S, Stucki F, Busato A, Kohler I. Analgesic effect of butorphanol and levomethadone in detomidine sedated horses. J Vet Med Assoc. 2001;48:337–342.

44. Schwartz CC, Hundertmark KJ, Lance WR. Effects of R51163 on intake and metabolism in moose. J Wildl Dis. 1991;27:119–122.

45. Sharma SK, Nigam JM, Singh M, Varshney AC, Kumar A. Sedative and clinic-biochemical effects of medetomidine in yaks (*Bos grunniens*) and its reversal by atipamezole. Ind J Anim Sci. 1998;68:236–237.

46. Tavernor WD. Anaesthetic procedures in the larger domesticated animals. Proc R Soc Med. 1960;53: 717–720.

47. Taylor PM, Browning AP, Harris CP. Detomidine-butorphanol sedation in equine clinical practice. Vet Rec. 1988;123:388–390.

48. Ven S, Schauvliege S, Gadeyne C, Gozalo-Marcilla M, Segaert S, Gasthuys F. Anesthesia with

α2 agonists in the llama: review and research. Vlaams Diergeneeskd Tijdschr. 2010;79:269–274.

49. Wiedner, EB, Lindsay, WA and Isaza, R. Management of zebras and zebra hybrids (zebroids). *Comp Yardley PA*; 2011;34:E4–E9. http://vetfolio-vetstreet.s3.amazonaws.com/6e/104c80ec7b11e1b0e6005056ad4735/file/PV0912_Wiedner_CE.pdf

50. Yamashita K, Tsubakishita S, Futaoka S, Ueda I, Hamaguchi H, Seno T, Katoh S, Izumisawa Y, Kotani T, Muir W. Cardiovascular effects of medetomidine, detomidine and xylazine in horses. J Vet Med Sci. 2000; 62:1025–1032.

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