Comparative cardiorespiratory and body temperature effects of ketamine-medetomidine, ketamine-xylazine, and ketamine-xylazine-diazepam anaesthetic protocols on the binturong (*Arctictis binturong*)

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Abstract

Here, we report retrospective data regarding cardiorespiratory and body temperature effects of anaesthetic protocols used on the binturong (*Arctictis binturong*), a viverrid species facing increasing threats from habitat loss and illegal trade. Between 2017 and 2024, 16 binturong (9 females, body mass 9.1–19.3 kg; 7 males, 12–18.7 kg) aged 1.5 to 20.5 years were anaesthetised on 38 occasions in a rescue centre in Laos using one of three anaesthetic protocols based on combinations of ketamine plus the α2 adrenergic receptor agonists medetomidine (n = 12) and/or xylazine (n = 20) plus diazepam (n = 6). No anaesthesia-related health problems or deaths were observed. Binturong administered different anaesthetic protocols showed no differences in time to observation of first signs of sedation (2–7 min) and onset of deep anaesthesia (3–39 min). Heart rate gradually decreased to bradycardia over the 75 min of anaesthesia with ketamine plus medetomidine and, while respiratory rate remained steady, males became hypothermic. Male body temperatures decreased even further when injected with ketamine plus xylazine. All three combined anaesthetic protocols proved safe and effective for repeated use. However, the cardiorespiratory and hypothermic effects observed suggest that medetomidine may be superior to xylazine. Nevertheless, perioperative body temperature monitoring and management will be imperative to prevent inadvertent temperature complications. Our findings improve understanding of binturong responses to anaesthesia and will have positive implications for wildlife veterinarians and conservation medicine.

Viverrids, dissociative anaesthesia, α2 adrenergic receptor agonists

The binturong (*Arctictis binturong*; also known as the bearcat), an elusive viverrid species native to Southeast Asia (Kleiman 1974; Francis 2019), is facing increasing threats due to habitat encroachment and illegal hunting (Corlett 2007; Willcox et al. 2016; Bourgeois et al. 2020). As a result, it has been designated as 'Vulnerable' by the International Union for Conservation of Nature (IUCN; Willcox et al. 2016) and is listed in Appendix III of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES 2014). These nocturnal mammals, with their unique prehensile tails and distinctive appearance (Kleiman 1974; Francis 2019), are increasingly threatened by deforestation, suburbanisation and agricultural expansion of palm oil and rubber tree plantations; hunting and poaching for meat or traditional medicine; and for their use in civet coffee farms (Rao et al. 2002; Willcox et al. 2016; Bourgeois et al. 2020; Honda et al. 2024). In addition, many rural communities both consume and trade wild animals, further threatening species such as the binturong. In particular, the illegal trade in wildlife between China and its neighbouring countries is increasing pressure on wildlife populations throughout these regions (Li and Wang 1999; Bell et al. 2004).

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The current binturong population in the wild is alarmingly low, with estimates suggesting that fewer than 10 000 individuals remain in their natural habitat across Indonesia, Malaysia, Vietnam, Myanmar and Laos (Willcox et al. 2016). In addition to the wild population, a significant number of binturong are kept in zoos and rescue centres worldwide, where they can play a crucial role in education and conservation (Gusset and Dick 2010; Bourgeois et al. 2020; Glatston and Duplaix 2020). However, the increased need to handle binturong for conservation purposes (Cosson et al. 2007) has raised concerns about the anaesthetic protocols used during veterinary procedures (Chinnadurai et al. 2016).

Use of anaesthesia is a crucial aspect of binturong veterinary care as it enables diagnostic and therapeutic procedures to be undertaken safely. However, choosing the best anaesthetic protocol is made more challenging by a lack of data on the effectiveness and safety of the different drugs available and the appropriate doses for this particular species (Moresco and Larsen 2003). The unique physiological characteristics of binturong necessitate tailored anaesthetic approaches to ensure their safety and well-being during medical interventions. In veterinary medicine, ketamine, a commonly used dissociative anaesthetic providing pain relief and sedation, is often used in combination with other drugs, such as medetomidine and xylazine. Medetomidine is an α2 adrenergic agonist used for sedation and analgesia, while xylazine, also an α2 agonist, is used as a muscle relaxant (Berry 2015; Rankin 2015; Whittem et al. 2015; Chinnadurai et al. 2016).

This study aims to address this lack of knowledge by comparing and evaluating use of three different anaesthetic protocols (ketamine-medetomidine, ketamine-xylazine and ketamine-xylazine-diazepam) in binturong at an animal rescue centre in Laos. In doing so, the study aims to identify the most effective anaesthesia protocol ensuring the well-being of binturong during complex veterinary procedures, thereby supporting successful breeding programmes and improving overall animal management, both in captivity and in the field (West et al. 2007; Chinnadurai et al. 2016; Fiorello et al. 2016). Several compelling factors underscore the necessity for this research. First, there is a significant lack of species-specific data regarding the anaesthetic needs of binturong (Moresco and Larsen 2003). Second, identifying the most effective protocols will enable veterinarians to perform required procedures with minimal risk (Belsare and Athreya 2010; Caulkett and Arnemo 2015). Third, improved veterinary care directly supports conservation goals, as healthier binturong are more likely to thrive, reproduce and contribute to genetic diversity, essential for sustainability and potential reintroduction efforts (Cosson et al. 2007; Greggor et al. 2018). We hypothesised that while all three combined anaesthetic protocols will be efficient in induction of a reliable chemical immobilization of binturong, it will be possible to recommend a superior protocol based on the comparison.

Materials and Methods

Animals and study area

In this study, we examined 16 adult binturong, chemically immobilised during routine procedures (e.g. physical examination, sample collection, surgical procedures or translocation) at the Lao Conservation Trust for Wildlife between 2017 and 2024 (Table 1). The test group consisted of nine females and seven males, all of which had been either rescued from the wild or from illegal captivity at sites across the Lao People's Democratic Republic (LPDR) and held in captivity for varying lengths of time. All animals were housed in 15 × 12 × 4 m enclosures. All were fasted for 12 h prior to anaesthesia, but with *ad libitum* access to water during this period.

Drugs and drug delivery methods

Three different anaesthetic combinations were used, the most frequently used (n = 20) being ketamine 100 mg/ml (Ketamine, Dutch Farm International BV, Nederhorst den Berg, Holland) with xylazine 100 mg/ml (Xylazine 10%; L.B.S. LABORATORY LTD., Bangkok, Thailand). The second most frequently used (n = 12) was ketamine 100 mg/ml with medetomidine 1 mg/ml (Sedator; Eurovet Animal Health BV, Bladel, Netherlands), followed by ketamine 100 mg/ml with xylazine 100 mg/ml and diazepam 5 mg/ml (Diazepam, State Enterprise Pharmaceutical Factory No. 3, Vientiane, LPDR) (n = 6). To reverse the effects of medetomidine and xylazine, atipamezole hydrochloride at a concentration of 5 mg/ml (Atipam, Eurovet Animal

Table 1. Sex, body mass, and age of binturong at the point of anaesthesia*.

Binturong No.	Sex	Body mass (kg)	1nd anaesthesia (age in yrs)	2nd anaesthesia (age in yrs)	3rd naesthesia (age in yrs)	4th anaesthesia (age in yrs)	5th anaesthesia (age in yrs)
1	female	9.1	1.5	1.5			
2	female	14	2	3			
3	female	14.4	2	3			
4	male	12	5				
5	female	15.3	9				
6	female	15.5	5	10			
7	male	12.8	17	17	17.5	18	
8	female	12.9	18	20.5			
9	female	19.3	6	11			
10	male	18.7	4.5	10			
11	female	14.8	8	10			
12	male	13.8	6	7.5	10	11	11
13	male	12.9	6	7	8	10	12
14	male	17.8	7				
15	male	16.3	5	11			
16	female	13	6	10	11		

*Some animals were anaesthetised on several occasions.

Health BV, Bladel, Netherlands) or yohimbine 10 mg/ml (Health Biochem, Xian, People's Republic of China) was used. For the ketamine-medetomidine protocol, the average atipamezole dose used to reverse the effects of medetomidine was 0.21 mg/kg, while for the ketamine-xylazine protocol, the average dose of atipamezole and yohimbine used to counteract the effects of xylazine was 0.01 mg/kg and 0.07 mg/kg, respectively. Finally, for the ketamine-xylazine-diazepam protocol, the average dose of atipamezole was 0.07 mg/kg.

The binturong were immobilized using a 3 ml volume dart administered by blowpipe intramuscularly to the gluteal muscles from a distance of ca 2–5 m, or by a pole syringe where animals were closer than 1.5 m.

Anaesthesia

The initial dose of anaesthetics was determined based on an estimate of the animal's body weight. Before entering the enclosure to handle the animals, the staff verified the animal's anaesthetic state by gently tapping it and checking for reflexes. The binturong was then placed in lateral recumbency and transported to the clinic (2–4 min driving by car), where they were weighed accurately. The anaesthetic dose was then recalculated in mg/kg based on the correct weight. Times of initial anaesthetic effects (sedation determined as uncoordinated walking and lying down) and onset time of deep anaesthesia (determined as complete loss of consciousness) were recorded. After recognition of deep anaesthesia, vital functions, such as respiratory and heart rates, body temperature and oxygen saturation, were monitored and recorded every 5 min throughout anaesthesia. Respiratory rate was assessed by monitoring thorax movements, while a digital thermometer (Omron Healthcare Eco, Brighton, United Kingdom) was used to obtain rectal temperature. Heart rate was monitored by pulse oximetry (UEM PM5000, Chongqing, People's Republic of China) and by auscultation of the heart, while oxygen saturation was monitored by pulse oximetry.

Following the procedure, the appropriate antidote was administered intramuscularly (atipamezole) or intravenously (yohimbine) and the individual was placed in a recovery cage for 2–3 h. After signs of full recovery from anaesthesia were observed, the animal was returned to its enclosure. The minimum washout period between anaesthesia events was 3 months; however, it was much longer in the majority of repeated immobilisation cases (Table 1).

Data analysis

All statistical analyses were undertaken using the TIBCO Statistica® software package v.14.0.0 (TIBCO Software Inc., USA). Physiological parameters of anaesthetised animals were compared using the Kolmogorov-Smirnov and Shapiro-Wilks tests, one-way analysis of variance (ANOVA) and the non-parametric Kruskal Wallis, Tukey's multiple comparison and Mann-Whitney U tests. Levels of statistical significance were set at either $P < 0.05$ or $P < 0.01$.

Results

Sixteen binturong, comprising nine females and seven males aged from 1.5 to 20.5 years with body mass ranging between 9.1 and 19.3 kg, and 12 and 18.7 kg, respectively, were anaesthetised on 38 occasions using the three anaesthetic protocols (Table 1).

Ketamine plus medetomidine anaesthetic protocol

First signs of sedation were observed in binturong within 2–7 min after administration of ketamine plus medetomidine, with deep anaesthesia onset ranging between 5–27 min (female avg. = 12.42, male avg. = 16.6 min). When recalculated for females and males, ketamine and medetomidine doses were 5.8–7.7 mg/kg (mean 6.24) and 3.9–11 mg/kg (mean 7.0), respectively, and 0.02–0.07 mg/kg (mean 0.03) and 0.02–0.08 mg/kg (mean 0.08), respectively.

Binturong heart rate (beats per min) decreased slowly over the 75 min of anaesthesia, with male and female heart rates only differing significantly ($P < 0.01$) at 55 min since onset of deep anaesthesia (Fig. 1). Compared against time 0 (i.e. onset of deep anaesthesia), mean heart rates (both sexes considered as one group) differed significantly ($P < 0.05$) at 15, 25, 35, 45, 50, 55, 65 and 70 min since onset. Respiratory rates remained relatively steady throughout the anaesthesia, with female and male rates only differing significantly ($P < 0.01$) at onset of deep anaesthesia, i.e. time 0 min (Fig. 2). Compared against time 0, mean respiratory rates (both sexes considered as one group) differed significantly ($P < 0.05$) at 20 and 25 min since onset (Fig. 2). Body temperatures of male binturong were generally lower than those of females throughout the 75 min of anaesthesia, only differing significantly ($P < 0.05$) at 40 and 45 min since onset (Fig. 3). Compared against time 0, mean body temperature (both sexes considered as one group) differed significantly ($P < 0.05$) at 20, 25, 35, 45, 50 and 55 min since onset.

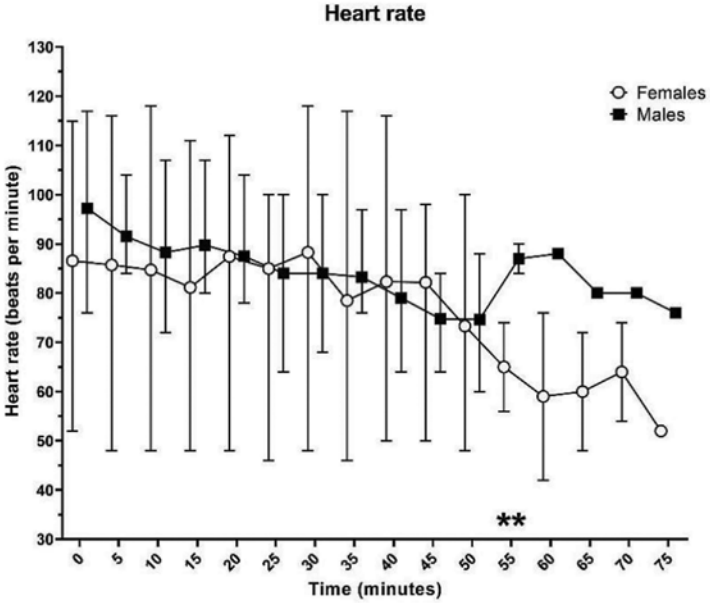

Fig. 1. Heart rate of binturong anaesthetised with ketamine and medetomidine (mean, minimum, and maximum). Females (n = 7) and males (n = 4) differed significantly (** = $P < 0.01$) at 55 min since onset of deep anaesthesia. Compared against time 0, mean heart rates for both sexes considered as one group differed significantly ($P < 0.05$) at 15, 25, 35, 45, 50, 55, 65 and 70 min since onset.

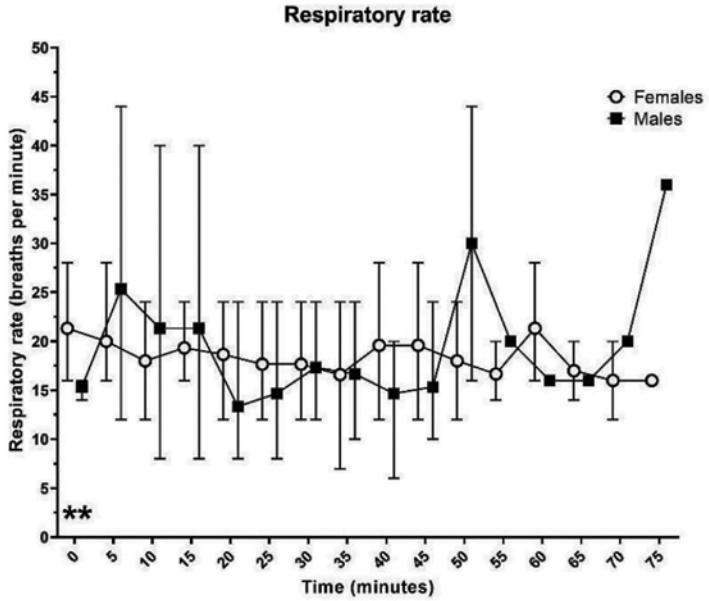

Figure 2. Respiratory rate of binturong anaesthetised with ketamine and medetomidine (mean, minimum, and maximum). Females (n = 6) and males (n = 3) differed significantly (** = $P < 0.01$) at onset of deep anaesthesia (time 0). Compared against time 0, mean respiratory rates for both sexes considered as one group differed significantly ($P < 0.05$) at 20 and 25 min since onset.

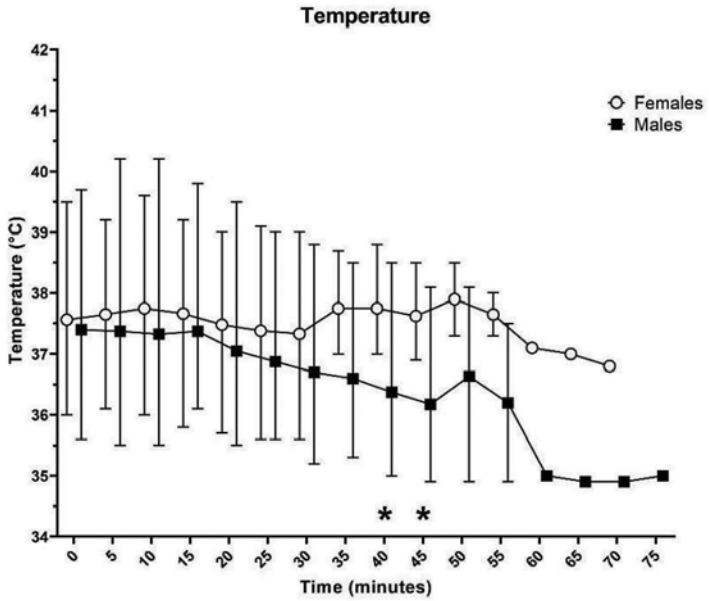

Fig. 3. Body temperature of binturong anaesthetised with ketamine and medetomidine (mean, minimum, and maximum). Females (n = 6) and males (n = 4) differed significantly (* = $P < 0.05$) at 40 and 45 min since onset of deep anaesthesia. Compared against time 0, mean body temperature for both sexes considered as one group differed significantly ($P < 0.05$) at 20, 25, 35, 45, 50 and 55 min since onset.

Ketamine plus xylazine anaesthetic protocol

First signs of sedation were observed within 3–5 min in binturong injected with ketamine and xylazine, with onset of deep anaesthesia following at between 3–39 min (female avg. = 11.33 min, male avg. = 12.3 min). When recalculated for females and males, the doses of ketamine and xylazine were 8.5–15.8 mg/kg (mean 13.5) and 3.0–35 mg/kg (mean 12.0), respectively, and 1.5–3.8 mg/kg (mean 2.9) and 2.0–4.0 mg/kg (mean 3.0), respectively

Heart rates in binturong males injected with either ketamine and medetomidine (K+M) or ketamine and xylazine (K+X) differed significantly over the 75 min of anaesthesia at 0 min since onset (K+M 97.25 ± 15.59, K+X 68.00 ± 8.76; $P < 0.01$), 15 min (K+M 89.75 ± 11.86, K+X 64.00 ± 4.38; $P < 0.01$), 30 min (K+M 84.00 ± 13.52, K+X 68.00 ± 4.38; $P < 0.05$) and 60 min (K+M 88.00 ± 0.00, K+X 67.00 ± 3.29; $P < 0.01$). In comparison, male respiratory rates over the 75 min of anaesthesia only differed significantly at 0 min since onset (K+M 15.33 ± 1.03, K+X 20.00 ± 4.38, $P < 0.05$). Body temperature values of males injected with ketamine and xylazine were significantly lower than those given ketamine and medetomidine throughout anaesthesia, excepting the last measurement at 75 min, with significant differences at 0 min since onset (K+M 37.40 ± 1.67, K+X 34.80 ± 0.11; $P < 0.01$), 15 min (K+M 37.37 ± 1.62, K+X 34.65 ± 0.05; $P < 0.01$), 30 min (K+M 36.70 ± 1.49, K+X 34.45 ± 0.05; $P < 0.01$), 45 min (K+M 36.17 ± 1.35, K+X 34.60 ± 0.22; $P < 0.05$), and 60 min (K+M 35.00 ± 0.01, K+X 34.30 ± 0.33; $P < 0.05$).

Ketamine plus xylazine and diazepam anaesthetic protocol

First signs of sedation after administration of ketamine plus xylazine and diazepam were observed within 3–5 min, with deep anaesthesia occurring 7–16 min after administration (female avg. = 11.5, male avg. = 12.0 min). Recalculation of doses for females and males resulted in 12.0–18.8 mg/kg (mean 15.27) and 12.6–16.0 mg/kg (mean 14.5), respectively, for ketamine; 1.0–1.3 mg/kg (mean 1.2) and 0.3–1.3 mg/kg (mean 1.03), respectively, for xylazine; and 0.5–0.6 mg/kg (mean 0.53) and 0.3–0.5 mg/kg (mean 0.4), respectively, for diazepam.

Discussion

In this retrospective clinical study, we report existing data obtained during anaesthesia of binturong using ketamine, medetomidine, xylazine and diazepam combined into three anaesthetic protocols. As the data were recorded over an eight-year period for reasons other than research, there was no elaborate study plan, and sample sizes and monitoring measurements differ for some animals, decreasing the rigour of analysis possible. Nevertheless, valuable information can still be obtained from this study. No anaesthesia-related health problems or deaths were observed in any of the test subjects during the study. Consequently, all three anaesthetic protocols appear safe and effective for repeated use in both male and female binturong aged between 1.5 to 20.5 years.

As most medicinal drugs are used in an extra-label manner for wildlife (AMDUCA 1994), any experience with anaesthesia of binturong may prove useful (Moresco and Larsen 2003). Indeed, dose-response data for anaesthetics are limited in many wildlife species (Lees et al. 2004). The outcomes and risks associated with wildlife anaesthesia depend on many factors and conditions over which veterinarians have only poor control (Kovacova et al. 2016). For example, in our own case, the health status of binturong was unknown at the moment of anaesthesia as there was no prior clinical examination, blood chemistry or haematology, making selection of appropriate drugs difficult. Furthermore, the body mass of the binturong could only be estimated prior to preparing the anaesthetic dose, meaning that the exact dose each animal received had to be recalculated following weighing after the individual was anaesthetised. While this may have resulted in a degree

of dose-related response variation, binturong administered different anaesthetic protocols showed no difference in either time to first signs of sedation or onset of deep anaesthesia. Recalculated dosage values also indicated that the drugs used had high therapeutic indices, and that the ketamine/medetomidine dose could be reduced to about one half of that necessary with ketamine/xylazine, which proved advantageous when reviving the animal using atipamezole, an α2 adrenergic receptor antagonist.

While the heart rate of binturong slowly developed bradycardia over the 75 min of anaesthesia with ketamine plus medetomidine, respiratory rates remained relatively steady, with males becoming hypothermic. Importantly, body temperatures of males injected with ketamine plus xylazine decreased more than with the ketamine plus medetomidine protocol. Despite known problems with attenuation of normal homeostatic thermoregulation imposing thermal stress (Imrie and Hall 1990), body temperature remains one of the least monitored vital parameters perioperatively (Bindu et al. 2017). As decreased body temperatures could prove detrimental for small mammals such as the binturong, it is important that veterinary anaesthetists remember to use devices to maintain perioperative normothermia. Interestingly, binturong body temperatures decreased during anaesthesia, even though the ambient temperatures under the tropical climate in Laos were relatively high (annual avg. 32 °C). As many binturong are held in captivity in zoos and rescue centres worldwide, we hypothesise that the lower ambient temperatures in more temperate locations may pose a higher risk of hypothermia when these animals are anaesthetised.

At present, there is only one other published article dealing with anaesthesia of binturong. Moresco and Larsen (2003) used a combination of medetomidine plus butorphanol plus a high (8 mg/kg, intramuscular) or low (2 mg/kg, intramuscular) ketamine dose and achieved comparable values for time to first signs of sedation and deep anaesthesia to our own study. On the other hand, there was no sign of bradycardia with these anaesthetic combinations and respiratory rates were low and associated with hypoxaemia, though body temperatures remained similar over time.

To conclude, all three protocols examined in this retrospective study proved safe and effective for binturong anaesthesia. Based on the observed cardiorespiratory and hypothermic effects, however, we suggest that medetomidine is superior and safer to xylazine. For veterinary use on binturong, perioperative body temperature monitoring and management is imperative to prevent inadvertent temperature complications such as prolonged recoveries due to slower anaesthetic drug metabolism and/or morbidity and mortality of the hypothermic patient. To extrapolate findings of the present study, while anaesthetic protocols tested here are supposed to be similarly effective in other closely related viverrids, smaller body mass makes these species probably even more susceptible to heat loss during anaesthesia. Future questions of viverrid anaesthesia will include, for example, longer-term effects of anaesthetics and the period necessary to exclude the influence of previous anaesthetic events, age and comorbidity related risk factors as well as determination of normal values for commonly monitored parameters.

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