The use of alfaxalone on free ranging African Pygmy Hedgehog (Atelerix albiventris) premedicated with xylazine produces a stable and short term anaesthesia

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SUMMARY

The African wild pygmy hedgehog has been domesticated and widely used in scientific experiments. Anesthesia of hedgehogs appear to be challenging, commonly associated with peri-anesthetic mortality. Inhalant anaesthetics are the agents of choice while injectable agents are seldom used and there are no reports on the use of alfaxalone. Thus the aim of this study was to evaluate two anaesthesia protocols of alfaxalone combined with a fixed dose of xylazine in hedgehog. Two groups consisting of 10 hedgehogs each were used in the study. The first group received 8mg/kg dose while the second group received 12mg/kg dose of alfaxalone with xylazine premedication maintained at 1mg/kg. All drugs were administered intramuscularly. Induction time, duration of anaesthesia and pain reflexes were monitored and recorded. Cardinal Health parameters were recorded just before, and at the 10^{th} and 20^{th} minutes post injection of anaesthetics. The two doses (8mg/kg and 12mg/kg) of alfaxalone used showed no differences on the induction time but induced profound anaesthesia that differed significantly ($P \leq 0.05$) and lasted for 37±14.72 and 54.4±17.35 minutes respectively with spontaneous and uneventful recovery. The two doses maintained respiration rates within the ranges of pre injection values while significant depression was noted on heart rates and rectal temperatures. The two tested doses of alfaxalone were well tolerated and appear to be safe for induction of short duration anaesthesia in hedgehogs. However, further study involving several doses to evaluate the cardiopulmonary dynamics and temperature regulation effects of the drug in question is recommended.

Key words: Alfaxalone, xylazine, anaesthesia, African pygmy hedgehog, *Atelerix albiventris*

INTRODUCTION

African Pygmy hedgehogs (*Atelerix albiventris*) are commonly encountered in the pet trade, although in many countries across the world they are highly controlled to limit potential disease risks (Heatley, 2005 and Heatley *et al.,* 2005). The African pygmy hedgehog or the four toed hedgehog is a nocturnal insectivore animal which is native to Central Africa. Recently, the animal has been domesticated and sold as exotic pet worldwide, and is also widely used in biomedical research. Consequently, many are being presented to veterinarians with diseases and husbandry-related disorders (Lennox, 2007). In Tanzania, hedgehog popularity as pet is low but the animals are increasingly collected for food. However, with increasing human population and influx of people from all over the world, the popularity of hedge hogs as pet is likely to rise. The growing demand for biomedical research and the emergence of diseases are likely to increase the value of hedgehog as laboratory animals. For effective medical care, the animals require chemical immobilization to facilitate examination due to their characteristic defensive rolling to form a ball-like appearance, also known as balling-up when startled. Furthermore, the spiny skin of hedgehog makes it challenging to handle and thus some form of anaesthesia becomes essential for appropriate handling and manipulation (Heatley, 2009).

Alfaxalone is a neuro-active steroid with anesthetic properties, approved in United States of America for use as induction agents in dogs and cats (NADA, 2018). It has, however, been used as anesthetic agent in domestic and wild (exotic) animals for over a

decade in many European countries, as well as Canada, New Zealand, and Australia (Hall and Clark, 1991). Alfaxalone is largely an intravenous agent, although intramuscular administration in fractious cats has shown to induce profound sedation and thus recommended under such circumstances when it appears to be reasonable (Tamura *et al*., 2015). Alfaxalone is largely intended for use as induction agent in animals, like other injectable anaesthetics such as propofol, etomidate and ketamine. Therefore, this study aimed at testing the potential use of alfaxalone for induction of anaesthesia in African pygmy hedgehogs after premedication with xylazine.

METHODOLOGY

Study area, animal capture and care

The present study was approved and carried out in accordance with Sokoine University of Agriculture Research Regulations and Guidelines. African Pygmy hedgehogs (n=20) used in this study were hunted, captured, and collected from the wild at night using a strong search light. Once spotted, the animal was slowly approached, handpicked and placed in a plastic basket ready to be taken to the temporary shelter where the animals were kept. The animals were kept for 24 hours to relieve them from capture stress before the experiment. 24 hours after anesthesia, the animals showed complete post-anaesthesia recovery and were released into their original habitat.

Evaluation of Alfaxalone Anaesthesia

One off observation on the effects of alfaxalone (Julox Pty NSW, Australia) and Xylazine (Inter Chemie, Holland) combinations on hedgehogs was conducted. Three doses of 4, 8 and 12mg/kg of alfaxalone were purposively selected based on the minimum and maximum doses available in literature (Bellini *et al*., 2019; Hawkins *et al*., 2020, Lennox, 2021, Doss and Carpenter, 2022) for other protocols employing alfaxalone as anaesthetic inducing agents in European and African hedgehogs whereas Xylazine was administered as described by Mori and O'Brien (1997). The experiment was conducted in two phases. During the first phase, 10 animals were divided into three groups (Figure 1A). The first group of 3 animals received 4mg/kg of alfaxalone combined with 1mg/kg of Xylazine (Inter Chemie, Holland). The second group of 3 animals received 8mg/kg of alfaxalone combined with 1mg/kg of Xylazine. The third group of 4 animals received 12 mg/kg of alfaxalone combined with 1mg/kg of Xylazine. The first phase of experiment was conducted to establish the minimum and maximum effective dose (Figure 1A). The second phase was conducted to evaluate additional clinical parameters. During the second phase, 20 animals were divided into two groups consisting of 10 animals each. One group received 8mg/kg and the second group received 12 mg/kg of alfaxalone combined with 1mg/kg of Xylazine respectively. Animals were weighed using a digital weighing scale; resultant weight was used to calculate the dosage of premedication (Xylazine) and alfaxalone prior to administration (Figure 2A). Injection of xylazine and alfaxalone was done according to the calculated dose by using insulin syringes via intramuscular route into obicularis panniculus muscle, in between the spines. After induction of anaesthesia eight parameters (Table 1) that determine adequacy of anaesthesia were determined and recorded.

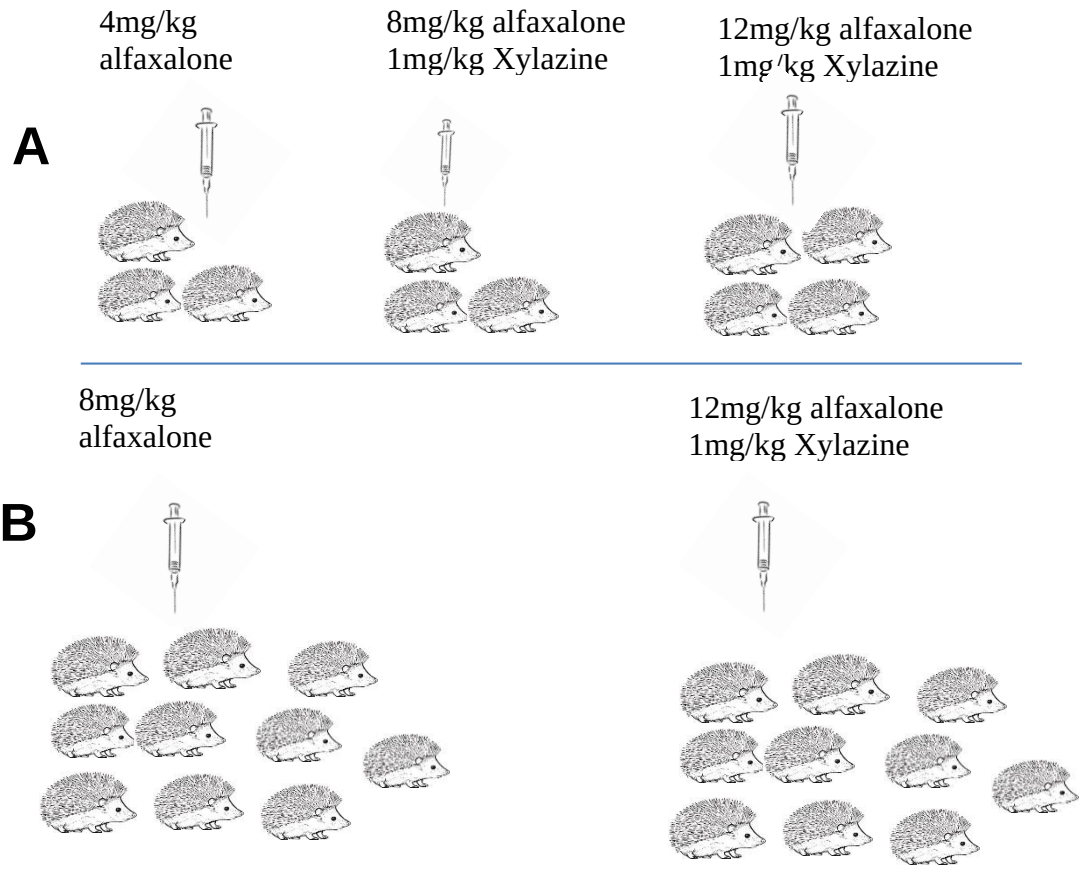

Table 1. showing different parameters recorded during alfaxalone anaesthesia in hedgehogs.

S/N	Parameter	Determination or measurement
1	Heart rate	measured by chest auscultation with a stethoscope
2	Respiration rate	measured by counting thoraco-abdominal movements
3	Rectal temperature	measured using digital thermometer inserted per rectum (Figure 2B)
4	Pupillary reflex	tested by flashing torch into the eyes
5	Toe pinch reflex	tested by pinching toe web with a hemostat forceps
6	Panniculus reflex	tested by needle prick on skin of the dorsal aspect of the animal
7	Jaw tone reflex	tested by opening the oral cavity using hemostat forceps (figure 3C)
8	Induction time and duration of anesthesia	calculated based on the timings recorded after administration of drugs and at recovery

Data analysis

The parametric values (for pre-anaesthesia and subsequent readings for the two protocols for the duration of anaesthesia, rectal temperature, heart and respiration rates) were recorded and entered into Microsoft excel sheets where the means and standard deviations of each parameter respective to their groups were calculated. The variations at each time within and between groups were compared as described by Sykes et al (1981) using the Students t-test modules available on excel. The confidence interval was set at 95%, hence P-values greater than 0.05 were considered significant.

RESULTS

During phase 1, animals ware only evaluated for the depth of anaesthesia achieved by injecting the respective amount of alfaxalone mixed with Xylazine. Animals given 8mg/kg and 12mg/kg alfaxalone showed profound anaesthesia and thus, selected for further evaluation of the drug effects on different

clinical parameters used for monitoring of anaesthesia reported in this study.

Induction and Monitoring of anaesthesia

The time from administration to induction of anaesthesia was noted and recorded in minutes and complete induction ensured when the animal showed fully unrolling (Figure 3 A & B). Adequate anaesthesia was judged as lack of protective reflexes namely pupillary, toe pinch, panniculus reflex and jaw tone reflex (Figure 3C). Duration of anaesthesia was defined as the time taken to recover from anaesthesia as noted from induction to when the animal showed complete recovery from anaesthesia.

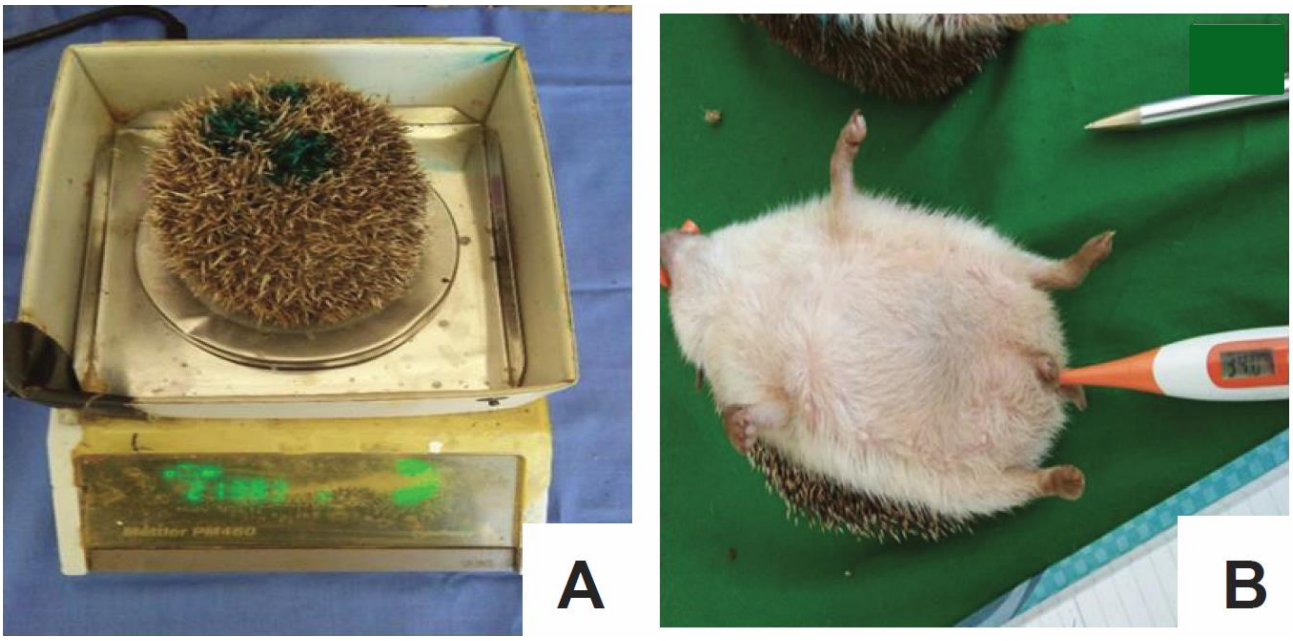

Figure 2. A: marked hedgehog being weighed using a digital scale, to calculate drug volume to be injected, and B: Measurement of rectal temperature during anaesthesia using a digital thermometer in a hedgehog

Figure 3. Stages of anaesthesia**: A:** Progressive unrolling as anaesthesia depth increases to surgical plane after alfaxalone injection**. B**: Completely Anaesthetized hedgehogs using the alfaxalone-xylazine protocol at 12mg/kg dose. **C**: Lack of jaw tone reflex after successful anaesthetization of hedgehog using alfaxalon

Effect of alfaxalone on the induction time and the duration of anaesthesia.

The average induction times were 4.8±2.86 and 5.3±3.06 for the 8mg/kg and 12mg/kg doses respectively (Table 2). From the table, the average duration of anaesthesia for the two doses was 37.6±14.72 and 54.4±17.35 for the 8mg/kg and 12mg/kg doses respectively with a significant inter group P value (Table 2).

Effects of alfaxalone on rectal temperature and cardio-pulmonary parameters

The study showed no variation in rectal temperature changes during induction (unrolling) between the two doses. However, each dose showed a significant drop in temperature from induction and subsequently until the animal recovered from anaesthesia (Table 3A). The temperature decline was nearly the same for the two doses given to hedgehogs. This means that dose dependent hypothermia was not present as both groups had drop in temperature almost to the same extent.

From Table 3B, the two doses induced a marked drop in the heart rate from the pre injection values and persisted for the entire observation period of twenty minutes. On the other hand, alphaxalone appeared to induce a dose dependent suppression of respiration rate. The suppression effects were manifested earlier during induction time and were more for the 12mg/kg dose (Table 3C). These differences persisted until the animal waked up. The time point differences on respiration rates within doses were not significant for the two doses protocol throughout the observation period (Table 3C).

Table 2. The induction time and duration of anaesthesia for the two doses of Alfaxalone in hedgehogs.

Time Interval (Minutes)	Dose injected		Between dose comparison
	8mg/kg dose (n=10)	12mg/kg dose (n=10)	
Induction time	4.8±.86	5.3±3.06	0.71ns
Duration of Anaesthesia	37.6±14.72	54.4±17.35	0.032*

Values are significantly different when P≤0.05 *

Table 3: Showing the effects of two doses of alfaxalone combined by 1mg/kg dose of xylazine on rectal temperature and cardio-pulmonary parameters in hedgehogs.

(A): Rectal temperature			
Time Interval (Minutes)	Within dose comparison		Between dose comparison
	8mg/kg dose (n=10)	12mg/kg dose (n=10)	
0	34.29± 0.55^{a}	34.29±0.33^{a}	1.0000^{ns}
10	33.79±0.67^{b}	34.01±0.25^{b}	0.35043^{ns}
20	33.45±0.72^{b}	33.71±0.29^{b}	0.30942^{ns}
(B): Heart rates			
0	174.8±22.87^{a}	155.2±13.44^{a}	0.03420^{ns}
10	147.6±8.33^{b}	143.2±13.31^{b}	0.54738^{ns}
20	137.6±13.36^{b}	137.6±12.40^{b}	1.00000^{ns}
(C): Respiration rates			
0	34±8.49^{a}	24.4±6.65^{a}	0.0119
10	31.6±9.70^{a}	20.4±5.48^{a}	0.00658*
20	31±9.72^{a}	20±5.96^{a}	0.00812*

Values showing different superscripts in a column are significantly different (P≤0.05)

DISCUSSION

In the present study, the two protocols employing different proportion of alfaxalone with a fixed amount of xylazine produced a more stable and short term anaesthesia (less than one hour) accompanied by uneventful recovery and, all vital parameters remained within safe ranges with a harmless drop in heart rates and rectal temperature. Artificial ventilation and warming of animal were not mandatory as all animal awakened without such support. The protocol described in this study provides comparable or better results to other existing anaesthesia protocols that include alfaxolone in pygmy hedgehog

anaesthesia. Bellini *et al.* (2019), Hawkins *et al*. (2020), Lennox (2021), and Doss and Carpenter (2022) describe the use of injectable anaesthetics utilizing different combinations including those of alfaxalone-midazolam, ketamine-midazolam, with or without reversal for a short duration induction of the light plane of anaesthesia in European (*Erinaceous europaeus*) and African (*Atelerix albiventris*) hedgehogs.

The combination of 2mg/kg alfaxalone and 0.05mg/kg Dexmedetomidine which was given intramuscularly induced anaesthesia in European hedgehog within 2 to 14 minutes and reversal was achieved by administration of Atipemazole. Additional sedatives and external sources of oxygen was required for heavier animals. Likewise, Hawkins *et al*. (2020) in a similar study using ketamine-midazolam and alfaxalone-midazolam achieved a light plane anaesthesia within 6 and 10 minutes for ketamine-midazolam and alfaxalone-midazolam anaesthesia which lasted for 19 and 14 minutes respectively after reversal with flumazenil.

Combination of 30mg/kg ketamine and 1mg/kg midazolam was compared with 3mg/kg alfaxalone combined with 1mg/kg midazolam (Lennox, 2021), results showed unpredictable anaesthesia for ketamine-midazolam but optimal sedation for alfaxalone-midazolam enough for clinical examination and radiological procedures in African pygmy hedgehogs. Elsewhere, a dose range of 3-5mg/kg alfaxalone and 1mg/g midazolam administered subcutaneously has been recommended for use in hedgehogs with partial reversal of midazolam by flumazenil given subcutaneously at a dose of 0.05mg/kg (Hawkins *et al.*, 2020, Doss and Carpenter, 2022). Literatures describing anesthesia in hedgehog favour inhalation anaesthesia including isoflurane, sevoflurane (Mori and O'Brien, 1997). Parenteral anesthesia is indicated for remote field work where logistics do not allow for inhalational agents.

Despite of its feasibility for remote or field application, Mori and O'Brien (1997) pointed out the tendency of injectable anaesthesia to induce prolonged recovery which is occasionally rough. Some protocols such as ketamine HCL at 5-20 mg/kg alone, or with diazepam at 0.5-2 mg/kg or xylazine at 0.5-1.0 mg/kg 1M have been successfully used (Mori and O'Brien, 1997). Xylazine (0.5-1mg/kg IM), and ketamine alone (20–30 mg/kg IM) or in combination with midazolam (1–2 mg/kg IM) had been reported to induce unrolling which facilitated examinations to be carried out. However, all the protocols discussed above appear to increase risk of hypothermia (Carpenter *et al.*, 2001) and cause prolonged recovery.

Dexmedetomidine and Medetomidine are superior to xylazine, and much more specific α_2-adrenergic receptor agonists but are seldom used in hedgehog and when injected intramuscularly at a dose of 0.05 to 0.2mg/kg induces profound sedation which require reversal (Bellini *et al.*, 2019). However, frequent adjustments of dexmedetomidine dose which appears to be necessary to achieve a particular clinical response may introduce uncertainties when designing a suitable protocol for field anaesthesia. In conclusion, the two protocols used in this study have shown good and promising results and can be used in African Pygmy hedgehog in situations where short term, profound anaesthesia is required to allow for short term surgical or clinical manipulations.

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CONFLICT OF INTEREST

Authors do not have any conflict of interest.

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