

Alfaxalone use in selected exotic species – part 1

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Alfaxalone is a synthetic neuroactive steroidal anaesthetic that achieves its central effects via interactions with gamma-Aminobutyric acid (GABA) receptors.



In a study of IV alfaxalone administration, respiratory depression and hypoxaemia were serious problems; therefore, oxygen supplementation should always be used.

It was first launched on the veterinary market in the 1970s along with another neurosteroid agent alfadolone; however, the vehicle (Cremophor EL, a castor oil-based surfactant) was responsible for severe allergic reactions that resulted in its withdrawal from the market (Jones, 2012).

Subsequently, alfaxalone has been used in a complex with cyclodextrin to achieve water solubility and form Alfaxan (Jurox), which was licensed for use in cats and dogs in Australia in 2000, the UK in 2007, central Europe in 2008, Canada in 2011 and the US in 2014 (Zeltzman, 2014). This formulation does not appear to be associated with histamine release or anaphylactic reactions, nor does it seem to cause irritation following perivascular or intramuscular injection (Jones, 2012).

Depending on the species and country-specific labelling, alfaxalone may be used IV and/or IM. If required, it may be diluted with lactated Ringer's solution or 0.9 per cent sodium chloride. Open vials should be discarded following the manufacturer's instructions (which may vary by country) as the bottle does not contain preservatives (Jones, 2012).

Alfaxalone is metabolised by the liver in most species, has a very short plasma half-life

(approximately 25 minutes in dogs and 45 minutes in cats) and a dose-dependent clearance (Jones, 2012; Lennox, 2015).

Depending on the species and country-specific labelling, alfaxalone can be used for IM sedation, premedication, as an IV induction agent, or for IV anaesthesia maintenance for very short procedures or over a longer period through constant rate infusion (CRI), irrigation techniques or multiple injections (Jones, 2012). There seems to be no increased adverse effects after repeated or prolonged use.

It can be used either alone or in combination with a variety of premedications, such as opioids, benzodiazepines, alpha-2 agonists, anticholinergics, phenothiazines, and NSAIDs – thus minimising the potential for respiratory and cardiovascular depression (Jones, 2012).

Although alfaxalone appears to facilitate muscle relaxation and has been documented to have some analgesic effects (causes transient, pre-emptive analgesia shortly after injection in rats), it is not considered an analgesic agent and is not adequate for painful procedures (Gilron and Coderre, 1996; Murison and Martinez Taboada, 2010; Zeltzman, 2014).

General anaesthetic gas does inhibit pain perception during its use, but does not inhibit nociceptive induction and transmission, which can lead to sensitisation of the nociceptive pathways. Therefore, an appropriate analgesic plan should be instituted (Zeltzman, 2014). Furthermore, as during any anaesthetic use, all patients should have IV access, fluid support and close monitoring.

Alfaxalone has a wide margin of safety, but is not free of side effects. It seems to have minimal cardiovascular effects at clinical doses, although it may decrease the cardiac output. IV injection may cause transitory apnoea in a variety of species, but these can be minimised by slow IV administration over 30 to 60 seconds to effect. Some species may also have a rough recovery when alfaxalone is used as a sole agent or in combination with a benzodiazepine only (Jones, 2012).

The manufacturer does not recommend combining Alfaxan with other IV anaesthetics and the drug should not be used in patients with a compromised liver function (Jones, 2012; Lennox, 2015).

Several reports exist in the literature about its use in a variety of exotic species and the aim of this article is to review some of these studies. Please refer to the literature for more in-depth information about this drug and its use in specific species.

Rabbits

Three studies have assessed the use of alfaxalone at different dosages as an IV induction agent in rabbits associated with the following premedications:

- morphine 1mg/kg or 2mg/kg IM and medetomidine 200µg/kg IM (with 10mg/kg loading dose of alfaxalone IV; Nevarrete-Caivo et al, 2014);
- fentanyl at 0.0125mg/kg IM and droperidol at 0.625mg/kg IM (with alfaxalone at 3mg/kg IV; Tutunaru et al, 2013); and
- buprenorphine 0.03mg/kg IM (with 2mg/kg and 3mg/kg alfaxalone administered over 60 seconds IV via a syringe driver; Grint et al, 2008).

In the first study, the combination of morphine and medetomidine, followed by anaesthetic induction with alfaxalone at the reported dosages, produced a suitable level of anaesthesia with a duration of action between 51 and 70 +/-21 minutes. However, animals experienced cardiorespiratory depression and a long period of apnoea.

The authors concluded it was advisable to provide oxygen after premedication and during alfaxalone anaesthesia, and endotracheal intubation and the application of intermittent positive pressure ventilation are mandatory after morphine/medetomidine/alfaxalone (at 10mg/kg IV) administration.

The second study similarly confirmed IV alfaxalone administration results in a smooth and rapid induction of anaesthesia in rabbits, allowing rapid intubation, but respiratory depression and hypoxaemia were serious problems. Therefore, oxygen supplementation during and after induction of anaesthesia should always be used.

In the study by Grint et al (2008), animals were preoxygenated before induction and intubated. Cardiopulmonary parameters remained stable during the anaesthetic period and the duration of apnoea was approximately 45 seconds. The recovery time was also rapid (approximately 35 to 40 minutes to standing).

Another study evaluated alfaxalone as a sole IV induction agent given slowly at 3mg/kg without premedication (Gil et al, 2014). This protocol resulted in rapid and smooth loss of consciousness. The righting reflex was lost in approximately 74 +/-34 seconds, while pedal withdrawal and ear pinch reflexes were lost at 120 +/-42 seconds after commencing IV administration. The duration of anaesthesia was approximately 8.9 +/-1.9 minutes, and the recovery was fast and uneventful once the animals obtained sternal recumbency.

Some data have shown alfaxalone appears to be effective when administered IM in cats and wild rabbits – bypassing the need for IV injection and the associated stress of handling (Marsh et al, 2009; Grubb et al, 2013), which may be particularly useful in exotic mammal practice.

Alfaxalone was studied as a single IM agent for sedation in the rabbit. Dosages investigated were 4mg/kg, 6mg/kg and 8mg/kg. Lower dosages appeared adequate for rapid (within four minutes of injection), smooth and short duration sedation, while 8mg/kg did not provide additional benefit (Huyh et al, 2015). The effect was deep enough to allow the loss of the righting reflex, but limb

withdrawal was present at all times, suggesting pain sensation was still present at all dosages and, therefore, additional analgesia required for invasive procedures.

IM administration of alfaxalone can provide a dose-dependent sedation, but with potential respiratory depression in rabbits. In the present study, apnoea was not seen at 4mg/kg and 6mg/kg; however, one of the 10 study animals that received an 8mg/kg dose had an episode of apnoea eight minutes after injection and died. Based on this episode, the authors discourage the use of this drug at 8mg/kg IM for sedation in rabbits until further data become available.

Rodents

Alfaxalone has been frequently used in laboratory rodents and found to provide reliable anaesthesia and some degree of analgesia (Gilron and Coderre, 1996). However, quite high doses have often been used and via routes that may not be appropriate for routine use in pet rodents.

A 2013 study investigated the pharmacokinetic properties of alfaxalone administered by intraperitoneal (IP) or IV injection (2mg/kg and 5mg/kg) in rats (Lau et al, 2013). Alfaxan given IP caused sustained levels of alfaxalone, no apnoea and longer sleep times than IV dosing, although immobilisation was not induced in 30 per cent of the laboratory animals.

Reports of IM administration of alfaxalone in combination with midazolam and an opioid in clinical practice exist (Lennox, 2015). This combination appears especially effective, safe and generally results in smooth recovery post-surgery in healthy rats undergoing elective neutering. The author prefers the use of midazolam at 0.5mg/kg, combined with an opioid of choice in a single syringe given IM, followed by alfaxalone at 2mg/kg to 3mg/kg IM.

Higuchi et al (2016) investigated the anaesthetic effects of alfaxalone in mice – administering it either alone at 100mg/kg or in combinations with 0.3mg/kg of medetomidine and 5mg/kg of butorphanol at doses of 20mg/kg, 40mg/kg, 60mg/kg or 80mg/kg. Each drug was given either IP or SC. Results suggest the combination medetomidine/butorphanol and alfaxalone at 60mg/kg given SC is suitable for inducing surgical anaesthesia in laboratory mice.

Schwenke and Cragg (2004) investigated the effects of four types of injectable anaesthetic regimens on laboratory guinea pigs' cardiorespiratory variables. In this experiment alfaxalone-alfadolone was used at an initial IV bolus dose of 4.5mg/kg slowly injected over 30 seconds, followed by an infusion rate of 9.75mg/kg/hr to maintain adequate anaesthesia.

It provided adequate anaesthesia, but only when the required dose was near the lethal dose. Additionally, the therapeutic index range for alfaxalone-alfadolone was narrow (for example, the correct infusion rate was often difficult to determine; anaesthesia fluctuated between light and deep levels).

In an old study, Green et al (1978) also evaluated the effect of IP or IM alfaxalone-alfadolone in several species. The authors found it only realised its full potential if given IV and considered it particularly valuable for the short-term anaesthesia of rats, mice and hamsters, having a wide safety margin in these species.

In rats, alfaxalone-alfadolone proved to show no tendency to tolerance and cumulation, and allowed stable anaesthesia for many hours. Respiratory complications were only encountered in guinea pigs.

Ferrets

Giral et al (2014) evaluated the anaesthetic effects of alfaxalone in ferrets. The neurosteroid was given either alone IV at 20mg/kg, 10mg/kg and 5mg/kg or IV at 2.5mg/kg in combination with IM medetomidine at 20µg/kg, or IV at 5mg/kg in combination with IM tramadol at 5mg/kg. Alfaxalone induced rapid anaesthesia and lateral recumbency at 5mg/kg and 10mg/kg, but the duration of anaesthesia and analgesia were shorter when 5mg/kg was used compared to 10mg/kg. This was considered sufficient only for brief sedation during non-painful procedures.

The medetomidine-alfaxalone combination produced longer duration anaesthesia and analgesia than alfaxalone administered alone at 5mg/kg. The combination allowed an adequate duration of anaesthesia and analgesia, while maintaining cardiorespiratory parameters at acceptable levels, was using medetomidine 20µg/kg and alfaxalone 2.5mg/kg.

When tramadol was administered, all the animals exhibited a strong excitation reaction and in no cases was the toe-pinch reflex clearly abolished. Thus, alfaxalone plus medetomidine provided safe and effective anaesthesia in ferrets. Alfaxalone on its own, or in combination with tramadol, did not produce satisfactory results for use as an anaesthetic for this species.

- **Please note, some drugs in this article are used under the cascade.**
- [Alfaxalone use in selected exotic species – part 2](#)

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