Alfaxalone; Alfaxan®

Hans Nieuwendijk

Nederland

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Alfaxalone is not a new drug. It was originally introduced in the 1970s as a mixture with alfadolone. The brand names were Althesin® for the human product and Saffan® for the veterinary market. Both products were withdrawn from the market because of severe adverse effects. These adverse effects (histamine release and anaphylactic reactions) were very probably caused by the solubilising agent Cremophor EL®, a derivate of castor oil.

Alfaxalone is remarketed as a water-soluble neuroanaesthetic. Water solubility was achieved by binding the alfaxalone-molecule to a cyclodextrine molecule. It is rapidly metabolized by the liver and does not cause histamine release like the former formulation. Alfaxalone's anaesthetic action is due to its binding to GABA-receptors.

With the introduction of Alfaxan® veterinarians have access to another anesthetic with a short and rapid duration of action with minimal side-effects. In general its clinical use and properties can be compared to propofol. Unlike propofol, alfaxalone has little or no cardiovascular effects when given in the normal dosage. At dosages of 20 mg/kg or more, cardiac output is diminished but this is well above the clinical dose[i,ii,iii].

Similar to propofol, alfaxalone is an induction agent that, because of its short half-life in dogs and cats, is very suitable for repeated bolus injections or a continuous rate infusion (CRI). Unlike propofol, alfaxalone does not show the lingering, potentially adverse effects when used repeatedly in close succession or as a longer duration CRI.

Alfaxan® can be safely combined with premedicants (xylazine, (dex)medetomidine, acepromazine, midazolam), opioids (morphine, methadone, hydromorphone, butorphanol, nalbuphine, buprenorphine, fentanyl), and NSAIDs.

Although in Europe Alfaxan® is registered only for intravenous injection and not for intramuscular administration, alfaxalone can be effectively delivered by the i.m. route in both cats and dogs. In Australia Alfaxan® is registered for i.m. use in cats. I.m. injection is not painful and onset of action is quick. Having access to this effective route of delivery is another major advantage of alfaxalone over propofol. Unfortunately, in larger dogs drug volume can be problematic.

There is some controversy regarding whether or not alfaxalone has analgesic properties. If it has, it surely plays a minor role and alfaxalone should not be considered a significant analgesic.

Unwanted side-effects:

1. Intravenous induction should be given very slowly; a period of apnea is commonly seen.
    a. The propensity for apnea to develop appears to be less than that seen with propofol.

2. When used as a sole agent, recovery can be rough. Balanced premeds will reduce or eliminate this unwanted effect[iv,v]. Cats seem to be extra sensitive to outside-stimuli and the recovery should be in a quiet, darkened room preferably.

Dosages:

Intravenous induction with alfaxalone is generally "to effect"; titrated to allow endotracheal intubation. The dosages below are guidelines and will decrease or increase depending on the premedications used and the degree of sedation evident at induction.

Induction

Induction dose	i.v.
Dogs	1 – 3 mg/kg (0.5 – 1.5 mg/lb)
Cats	2 – 5 mg/kg (1 – 2.5 mg/lb)

Because of its minimal influence on cardiac output, alfaxalone can be used in compromised/injured patients. The intramuscular route can be a very effective way to sedate 'high-risk' patients that find physical restraint for i.v. catheter placement excessively stressful. For instance a cat after it has been hit by a car, an obstructed male cat or a very anxious small breed dog in which you don't want to use other sedatives. Within minutes, alfaxalone can make an anxious, fearful and stressed cat or small dog into a meek and relaxed patient that will tolerate IV catheterization, examination, and treatment safely (for both patient and doctor).

For this indication alfaxalone should not be used alone; alfaxalone should be combined with midazolam. We can reduce the stress caused by physically restraining such an animal enormously. In this type of scenario, alfaxalone is being used less as an induction agent than as a procedural sedative (similar to treating a patient with low doses of ketamine i.m.). Drug effect typically peaks in 5 minutes and, in the dog, the sedation period is quite short; you need to proceed with catheter placement quickly and efficiently.

In Australia alfaxalone is registered for i.m. use in cats. In dogs alfaxalone can also be used i.m. under the following conditions.

Key I.M. Sedation Points in Dogs

- Do not give alfaxalone alone, combine it with midazolam.
- Due to the volume needed and the fact that alfaxalone is rapidly metabolized, this application of alfaxolone is limited to smaller dogs (< 10 kg).
- The sedation that is achieved will be of short duration but will provide the time to get i.v. access, draw a blood sample or take an X-ray if you are quick and efficient.
- Recovery can be very restless so additional medication (which can now be given i.v.) or a CRI is necessary.
- Alfaxalone i.m. should NOT be used to sedate an aggressive and otherwise healthy dog. There are better and more reliable means to do this.

I.M. sedation	alfaxalone	midazolam
Dog /cat	2 – 4 mg/kg (1 – 2 mg/lb)	0.3 mg/kg (0.15 mg/lb)

Maintenance;

This is also too effect; titrated to patient need and very dependent on the type and clinical effect of premedication used. Again when (dex)medetomidine is used (especially in conjunction with an opiod) the lower dose range should be used[vi,vii].

Maintenance	CRI
Dogs	4 – 7 mg/kg/hr (2 – 3.5 mg/lb/hr)
Cats	5 – 8 mg / kg / hr (2.5 – 4 mg/lb/hr)

Special comments;

- Alfaxalone has no effects on neonates when used as an induction agent for caesarian section[viii].
- Alfaxalone can replace etomidate as an induction agent for high risk patients.
- Alfaxalone is a suitable agent for sighthound anaesthesia[ix].
- When administered to feline patients repeatedly or continuously over time as a CRI/MCI, alfaxalone does not have the problematic cumulative effects that are typically associated with propofol.
- Alfaxan® contains no preservatives. Opened bottles should be handled with caution.
    - Labeling in New Zealand and Australia states:
        - "STORAGE: Store below 30°C (Room Temperature). Protect from light. Alfaxan-CD RTU Anaesthetic Injection contains no preservatives. Solution should be removed from the vial using aseptic technique. Contents of broached vials should preferably be used within 24 hours, but may be stored if necessary at 4°C for up to 7 days provided contamination is avoided. Do not use broached vials if the solution is not clear, colourless and free from particulate matter."
    - Labeling outside of New Zealand and Australia states:
        - "6.3. Shelf life: Shelf life of the veterinary medicinal product as packaged for sale: 30 months. This product does not contain an antimicrobial preservative. Any solution remaining in the vial following withdrawal of the required dose should be discarded."
- For use in smaller patients it may be best to dilute the alfaxalone 10 mg/ml to 5 mg ml, using equal volumes of Lactated Ringers solution or 0.9% NaCl. This allows for more precise dosing and adjustments.

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[i] The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. Muir W, Lerche P, Wiese A, Nelson L, Pasloske K, Whittem T. Vet Anaesth Analg. 2009 Jan;36(1):42-54.

[ii] Cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in dogs. Muir W, Lerche P, Wiese A, Nelson L, Pasloske K, Whittem T. Vet Anaesth Analg. 2008 Nov;35(6):451-62. Epub 2008 Sep 11.

[iii] Plasma pharmacokinetics of alfaxalone in dogs after an intravenous bolus of Alfaxan-CD RTU. Ferré PJ, Pasloske K, Whittem T, Ranasinghe MG, Li Q, Lefebvre HP. Vet Anaesth Analg. 2006 Jul;33(4):229-36.

[iv] Clinical evaluation of Alfaxan-CD(R) as an intravenous anaesthetic in young cats. Zaki S, Ticehurst K, Miyaki Y. Aust Vet J. 2009 Mar;87(3):82-7.

[v] Induction of anaesthesia with alfaxalone or propofol before isoflurane maintenance in cats. Taboada FM, Murison PJ. Vet Rec. 2010 Jul 17;167(3):85-9.

[vi] The pharmacokinetics and pharmacodynamics of alfaxalone in cats after single and multiple intravenous administration of Alfaxan at clinical and supraclinical doses. Whittem T, Pasloske KS, Heit MC, Ranasinghe MG. J Vet Pharmacol Ther. 2008 Dec;31(6):571-9.

[vii] Comparison of the anesthetic efficacy and cardiopulmonary effects of continuous rate infusions of alfaxalone-2-hydroxypropyl-beta-cyclodextrin and propofol in dogs. Ambros B, Duke-Novakovski T, Pasloske KS. Am J Vet Res. 2008 Nov;69(11):1391-8.

[viii] Jurox Study (JX9604.03-C016) A multi-centre clinical trial evaluating the efficacy and safety of Alfaxan®-CD RTU administered to dogs for induction of anaesthesia prior to Caesarean section.

[ix] Plasma pharmacokinetics of alfaxalone in both premedicated and unpremedicated Greyhound dogs after single, intravenous administration of Alfaxan at a clinical dose. Pasloske K, Sauer B, Perkins N, Whittem T. J Vet Pharmacol Ther. 2009 Oct;32(5):510-3.