Reintroduced Anesthetic Alfaxalone

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Alfaxalone, a neuroactive steroid with anesthetic properties, has recently been approved for induction and maintenance of anesthesia in dogs and cats in the United States after being approved for several years in many European countries, Canada, and Australia. Although alfaxalone is a steroid molecule, it has not been shown to have glucocorticoid or mineralocorticoid actions. The anesthetic properties of alfaxalone are a result of its effects on $GABA_A$ receptors in the CNS, making the receptors more sensitive to the effects of inhibitory neurotransmitter GABA, enhancing chloride ion transport, and hyperpolarizing neuronal cell membranes.

Alfaxalone is not a new drug; it was previously used in 1971 as 1 of 2 compounds in an anesthetic for animals (Saffan).[1] In that historic anesthetic, a castor oil surfactant (Cremophor EL) used to dissolve the alfaxalone (a hydrophobic molecule) was responsible for many adverse effects, which led to its removal from the market.[2-4] These issues have been resolved with the use of a cyclodextrin, a non-irritating and non-histamine–releasing carrier agent, to solubilize the alfaxalone.

Alfaxalone is now commercially available as a 1% (10 mg/mL) aqueous solution in hydroxypropyl-β-cyclodextrin, under the trade name Alfaxan (alfaxan.com). Unlike propofol, alfaxalone is a colorless and clear agent. The formulation has no preservatives, and the label recommends that any unused portion of the product be discarded within 6 hours from initial vial opening in order to minimize the risk of contamination. Alfaxalone is considered a class IV controlled substance by the United States Drug Enforcement Agency.

Alfaxalone generally produces smooth, rapid induction of anesthesia. Its cardiovascular and respiratory effects seem to be similar to those of propofol with slightly less respiratory depression. It can be used in sight hounds, and it is not arrhythmogenic. Because of its rapid metabolism, alfaxalone has minimal cumulative effects and can also be used for maintenance of anesthesia without adversely prolonging recovery.

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Administration

As with most anesthetic induction agents, alfaxalone should be slowly administered IV to effect (>60 seconds) so that blood and brain drug concentrations have time to reach equilibrium. Slow titration avoids administration of excessive (and unnecessary) amounts of the drug and minimizes adverse respiratory and cardiovascular effects, which are typically dose-dependent.

Recommended doses for healthy and unpremedicated dogs and cats are 2 and 5 mg/kg, respectively.[5,6] However, use lower doses in older or compromised patients. As with any induction agent, premedication with sedative or analgesic agents as well as adding benzodiazepines and/or opioids to the induction protocol will further reduce the required anesthetic dose of alfaxalone (1-2 mg/kg for dogs and 2-4 mg/kg for cats, always titrated to effect).

Induction of anesthesia with alfaxalone is typically smooth, but some excitement and muscle twitching are occasionally seen. Similar to propofol, respiratory depression with potential apnea and oxygen desaturation may occur if the drug is administered too rapidly or if a high dose is used. Respiratory depression seems to be less likely with alfaxalone than with propofol, provided equipotent anesthetic doses are used.[7] It is recommended that patients be pre-oxygenated with 100% oxygen prior to anesthetic induction to minimize risk for hypoxemia. Endotracheal intubation equipment, supplemental oxygen, and ventilation assistance must be readily available.

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Cardiovascular effects of alfaxalone include increased heart rate, decreased systemic vascular resistance, and likely decreased myocardial contractility, which may lead to decreased arterial blood pressure. These effects are dose-dependent and are considered mild at clinical doses. The addition of inhalation anesthetics may further compound these effects and hypotension is possible. Attentive monitoring must be employed during transition into inhalant anesthesia so rapid detection and appropriate treatment can be instituted.

Indications

Alfaxalone is most commonly used to provide IV induction of anesthesia prior to maintenance with inhalant anesthetics but can also be used as a maintenance agent in cases where total IV anesthesia may be preferred (eg, bronchoscopy, tracheal laceration, severe intracranial disease).

Alfaxalone has a fairly rapid onset of action (60 seconds) and short duration. In unpremedicated dogs, without noxious stimulation, a single dose of 2 mg/kg IV provides about 10 minutes of anesthesia (from induction to extubation), while in cats, a single dose of 5 mg/kg IV provides a longer period of anesthesia—approximately 25 minutes from induction to extubation.[5,6] Duration of anesthesia can be safely prolonged by premedication, through administration of subsequent boluses (about 1 mg/kg) or by continuous infusion without excessively prolonging recovery time. Constant rate infusion values are not well-established but range from 5-10 mg/kg/h in cats and 4-7 mg/kg/h in dogs and should be adjusted to patient needs.

Alfaxalone may be particularly useful in cats where longer periods of IV anesthesia are required, as, unlike propofol, use of alfaxalone as a continuous infusion does not seem to be associated with excessively prolonged anesthetic recoveries in this species.[8,9] Be aware, however, that cats take longer than dogs to recover from alfaxalone, even after a single dose.

Although not licensed for IM or SC use in the United States, alfaxalone has been used by those routes to provide stressed, anxious cats mild to heavy sedation, which is typically enough to obtain IV access or perform other simple procedures (eg, blood collection, diagnostics).[10-12] However, IM and SC injections of alfaxalone are associated with prolonged recoveries characterized by agitation and hypersensitivity to stimuli.[11] Addition of a sedative and an opioid helps reduce the dose of alfaxalone and extends duration of effect. The combination also improves the quality of recovery, attenuating excitement that can be seen when only alfaxalone is used. Intramuscular use of alfaxalone is limited by the large volume of injection and thus is restricted to smaller patients (cats, rabbits, ferrets, and other exotic patients [eg, iguanas, turtles]). IM administration does not cause tissue damage, although some cats resist the injection. At doses of 2.5-5 mg/kg IM, cats achieved maximum sedation at approximately 10-15 minutes, while with SC administration of 3 mg/kg (with butorphanol at 0.2 mg/kg), peak effect was only reached by 30-45 minutes postadministration.[10,12] IM use in dogs is not recommended because of the large volumes of injection and potential for undesirable recoveries (paddling, vocalization, and muscle tremors).[13]

Alfaxalone's short duration of action is a result of rapid metabolism in the liver. Its rapid elimination and lack of significant cumulative effects make alfaxalone well suited for use as a continuous infusion. Initial studies suggest that alfaxalone may be administered repeatedly over a day or several days without significant adverse effects,[14,15] which makes it particularly beneficial for cats requiring repeated anesthesia (eg, wound management, radiation therapy). Cats have a limited ability to metabolize propofol, which in turn can lead to adverse effects after prolonged or repeated administration. However, further study is needed to support the safety of repeated administration, particularly in animals with compromised liver function.

Disadvantages & Adverse Effects

The most common adverse effects are respiratory depression and apnea, which is similar to propofol, and associated with dose and speed of administration. The patient should be monitored continuously, and the clinician must be prepared to secure the airway and support ventilation if needed.

Excitement can occur during recovery, as patients may awaken from anesthesia quickly, especially when alfaxalone is used alone in unpremedicated patients. Agitation, paddling, muscle fasciculations, and exaggerated reaction to external stimuli have been seen on occasion, particularly in cats. It is recommended that cats recover from anesthesia undisturbed in a quiet, dark environment to minimize stimulation and excitation.

Alfaxalone has no analgesic properties, and therefore analgesic drugs must be included in the anesthetic protocol if procedures that may elicit pain or discomfort are to be performed.

Drug Interactions

Alfaxalone can be safely used in combination with all routinely used sedatives (acepromazine, α_2-agonists), analgesics (opioids, NSAIDs), and other adjunct drugs (benzodiazepines, anticholinergics). The degree of preanesthetic sedation, as well as the addition of adjunct drugs to the induction and maintenance protocol, effectively reduces the required dose of alfaxalone and significantly prolongs its duration of effect. Some adverse effects

may be exacerbated by these drug combinations (depth of anesthesia, respiratory depression, apnea).

Advantages

Alfaxalone induction quality is similar to propofol but does not cause discomfort during IV administration. In its current formulation with cyclodextrin as a solubilizing agent, alfaxalone is not associated with histamine release. Studies suggest that it can be safely used as an induction agent for cesarean deliveries with minimal depression of the neonates and in sight hounds.[16] In addition, no adverse effects have been reported when alfaxalone was used for induction of anesthesia in puppies and kittens younger than 12 weeks old.[17,18] Alfaxalone has already been used IM and IV in rabbits and tortoises/turtles and IM in iguanas and marmosets with mostly favorable results,[19-23] suggesting that it can also be a very useful drug for sedation and anesthesia of exotic patients.

Economic Impact

Alfaxalone is more expensive than other induction agents currently available in clinical practice, but because of its versatility and favorable characteristics, it will likely become a popular anesthetic agent for small animals (and likely for exotic companion pets) in the United States. Similar to any induction agent, the routine use of preanesthetic sedation in combination with other adjunct drugs (eg, benzodiazepines, opioids) will help reduce the required dose of alfaxalone, the overall cost, and the common side effects. ■ cb

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