Alfaxalone (3α-hydroxy-5α-pregnan-11,20-dione) is a synthetic neuroactive steroid used to induce and maintain general anesthesia. The anesthetic properties of alfaxalone have been known since 1971, and this drug was first marketed in the 1970s as Althesin (by the former Glaxo Laboratories Ltd., Greenford, Middlesex, UK) and Saffan (by the former Schering Plough Animal Health, Welwyn Garden City, UK) for human and veterinary anesthesia, respectively. This original formulation was combined with alfadolone, another neurosteroid with weak anesthetic properties, and dissolved in 20% polyoxyethylated castor oil (Cremophor EL; BASF Corp., basf.com). However, in cats, this vehicle caused serious reactions such as hyperemia, edema of the pinnae and distal thoracic limbs, partial laryngeal spasm, and cyanosis. In dogs, common adverse effects included salivation, rhinorrhea, edema of the paws and eyelids, hypotension, pulmonary edema, and anaphylactic reaction caused by histamine release. For these reasons, in 2002 Saffan was discontinued and removed from the market. In the United States, Saffan was never approved by the Food and Drug Administration (FDA) and was never available for use in veterinary medicine. Meanwhile, a new alfaxalone formulation, called Alfaxan, was released in Australia in 2001, in Europe in 2007-2008, and in Canada in 2011. It became available in the United States in 2012 and was approved by the FDA for induction and maintenance of anesthesia in dogs and cats. This new formulation, sold and distributed by the Australian company Jurox Animal Health (jurox.com/au), is a sterile clear aqueous solution with a pH of 6.5 to 7.0, containing a noncremophor vehicle (2-hydroxpropyl-β-cyclodextrin), which does not cause histamine release. Until June 2018, Alfaxan was available in the United States only in a 10 mL vial with no preservative and with a shelf life of 6 hours after first use. Although this product may still be available, the company is discontinuing its production and has replaced it with a new multidose formulation that contains 3 preservatives: ethanol, benzethonium chloride, and chlorocresol. The multidose formulation seems to have the same efficacy and safety as those without preservative, but the advantage is that the multidose formulation has a shelf life of 28 days after first use. Multidose alfaxalone is available in 10 mL and 20 mL vials.

**MECHANISM OF ACTION**

Alfaxalone produces unconsciousness by acting on the gamma aminobutyric acid subtype A (GABA_A) receptors in the central nervous system (CNS). These receptors are ionotrophic ligand-gated channels, and GABA is their endogenous ligand. GABA is the main inhibitory neurotransmitter in the CNS. After the receptor is activated, the channel opens and promotes...
chloride conduction into the cell, causing hyperpolarization of the postsynaptic membrane. At low concentrations, alfaxalone positively modulates chloride current through the chloride channel; but at higher concentrations, it functions as a GABA agonist, in the same way as barbiturates. The end result is profound sedation or induction of anesthesia, depending on the dose and route of administration.

**CLINICAL USES AND INDICATIONS**

Similar to propofol, alfaxalone has a rapid onset of action, provides satisfactory muscle relaxation, and is not associated with accumulation after repeat dosing. In the United States, the preservative-free preparation was labeled for intravenous (IV) administration only; however, in other countries, it was approved for intramuscular (IM) administration. Alfaxalone has been administered intramuscularly to dogs and cats, and several studies have administered it intraperitoneally to laboratory animals. The 28-day formulation is labeled for IV use only, and it appears that Jurox will not pursue FDA approval for IM administration. Although no safety or efficacy data have yet been published on the IM route of the formulation with preservative, I believe that veterinarians are using it via this route, as they had used the previous formulation, and getting the same results.

**FDA-Approved Dosages and Uses**

For dogs that do not receive any premedication, induction of anesthesia with alfaxalone is achieved with a dose range of 1.5 to 4.5 mg/kg (average 2.2 mg/kg) administered intravenously to effect. In cats this dose is higher, ranging from 2.2 to 9.7 mg/kg (average 4 mg/kg). Although alfaxalone is approved for induction without premedication, I discourage use of this technique. This drug does not provide any analgesia; for patients undergoing invasive procedures, preemptive and postoperative pain management must be considered. Moreover, for some animals, recovery from alfaxalone anesthesia can be rough if no other drugs are used; reported events include paddling, vocalization, rigidity and myoclonus in dogs and paddling and trembling in cats.

Alfaxalone can be used with several sedative and/or analgesic agents. The following agents have been used to sedate dogs and cats before administration of alfaxalone: opioids (e.g., morphine, fentanyl, methadone, buprenorphine, butorphanol), alpha-2 agonists, benzodiazepines, and acepromazine. In premedicated dogs, the dose of alfaxalone required to induce general anesthesia ranges from 0.5 to 3.0 mg/kg and in cats from 3.0 to 4.0 mg/kg.

Alfaxalone can also be used to maintain general anesthesia. The label mentions only that maintenance can be achieved by intermittent IV boluses, although constant rate infusion (CRI) regimens have been used in dogs and cats. For nonpremedicated patients, the recommended bolus dosage is 1.5 to 2.2 mg/kg every 6 to 8 minutes for dogs and 1.4 to 1.5 mg/kg every 3 to 5 minutes for cats. For premedicated patients, the dosage decreases to 1.2 to 1.4 mg/kg every 6 to 8 minutes for dogs and 1.1 to 1.3 mg/kg every 7 to 8 minutes for cats.

**Extralabel Use**

As previously mentioned, alfaxalone has been administered to dogs and cats by the IM route. This route is advantageous when dealing with aggressive animals and when induction of general anesthesia needs to be achieved without an IV catheter. When given via the IM route, alfaxalone can be mixed in the same syringe with sedative drugs, such as opioids, alpha-2 agonists, and midazolam. The only other induction drugs that can be used effectively via the IM route are the phencyclidine derivatives, such as ketamine. The advantage of alfaxalone over ketamine is that IM injection is not painful because of its neutral pH (alfaxalone pH 6.5 to 7.0 vs ketamine pH 3.5 to 5.5). The disadvantage of alfaxalone is the larger volume required to induce general anesthesia when administered via the IM route, which can be a limiting factor. For example, if 4 mg/kg of alfaxalone is required for a 5-kg cat, the volume will be 2 mL without any other drug added to it. To overcome this limitation, I use approximately 1.0 to 1.5 mg/kg of alfaxalone mixed with either one of the following drugs or a combination: dexmedetomidine, an opioid (e.g., hydromorphone), and midazolam. The dose of the sedatives and analgesics mixed with alfaxalone varies according to demeanor and health status of the patient and desired duration of sedation. The ranges of doses I have used are 2 to 8 mcg/kg of dexmedetomidine, 0.05 to 0.1 mg/kg of hydromorphone, 0.2 to 0.4 mg/kg of butorphanol, and 0.2 to 0.4 mg/kg of midazolam. These drug combinations average an approximate volume of 1 mL for a 5-kg cat. When these combinations are administered via the IM route, they cause mild to profound sedation that enables placement of an IV catheter and performance of noninvasive or minimally invasive procedures (e.g.,
radiography, abdominal ultrasonography, fine-needle aspiration, and small skin biopsies). This sedation usually lasts 20 to 40 minutes, depending on the drugs and dosages used in combination with alfaxalone. If general anesthesia is required, 2 to 3 mg/kg of alfaxalone (or any induction agent) can be administered intravenously after the catheter is in place.

In terms of general anesthesia maintenance, the label specifies only use of intermittent boluses to maintain an adequate plane of anesthesia with alfaxalone; however, CRI regimens can also be used. In dogs, after premedication and anesthesia induction with different drugs, anesthesia can be maintained with doses of 0.16 to 0.2 mg/kg/min.⁶,³⁶,³⁷ and in cats, 0.12 to 0.2 mg/kg/min.⁸,²²,³⁸,³⁹ These CRI doses should be considered as a starting point for maintenance of general anesthesia, and adjustments should be based on the patient’s response. To decrease the dose of alfaxalone needed, other sedative/analgesic drugs (e.g., alpha-2 agonists and opioids) can be administered to the anesthetized patient as a bolus or CRI. A recent study reported poor recovery scores when anesthesia in dogs was maintained with alfaxalone CRI for a prolonged period (210 minutes); however, those authors concluded that the choice of premedication protocols and demeanor of the animals might have influenced these results.³⁷ Other studies have shown that when alfaxalone CRI is used for 85 to 130 minutes after adequate sedation, the quality of the recovery ranges from good to excellent.⁶,²⁵,³⁴

CAUTIONS

Respiratory Depression
Alfaxalone causes respiratory depression even at recommended doses; apnea has been observed, especially after rapid IV administration.⁸⁰ The anesthetist should always be prepared to intubate the patient, even when lower doses and/or the IM route are used. To prepare for apnea or marked respiratory depression, the clinician should have readily available an endotracheal tube and a laryngoscope. Because of this adverse effect, preoxygenation and oxygen supplementation (i.e., flow-by) are advised even for patients that are sedated only.

Cardiovascular Depression
The effects of alfaxalone on the cardiovascular system are similar to those of propofol.¹⁷,⁴¹ At the time of induction, increased heart rate and decreased blood pressure can be observed; however, mild hypertension can also occur. Overall, when the recommended doses are used, the cardiovascular parameters tend to remain within normal limits.³⁷

Potential for Abuse
Alfaxalone causes CNS depression, and the potential for abuse is equivalent to that of midazolam and diazepam. For this reason, the US Drug Enforcement Administration classifies alfaxalone as a Controlled Schedule IV substance, similar to benzodiazepines. This classification means that although alfaxalone has an accepted medical use, its abuse may lead to physical or psychological dependence. Like other controlled substances, alfaxalone must be securely stored, its use must be logged, and its disposal must be performed according to federal regulations.

SUMMARY
Alfaxalone has been used to induce general anesthesia for many years, but only recently has a new formulation with preservatives become available in the United States. This formulation has a shelf life of 28 days after first use. It is approved for IV administration to induce and maintain general anesthesia in dogs and cats; however, it is also used via the IM route for induction and sedation (off label). Alfaxalone is less painful than ketamine when injected via the IM route. Respiratory depression and apnea are possible; when only sedation is planned, supplemental (flow-by) oxygen should be provided and the anesthetist should be prepared to intubate and provide ventilatory support if needed. TVP

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