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Review

A review of the pharmacology and clinical application of alfaxalone in cats

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ABSTRACT

Alfaxalone-2-hydroxpropyl-β-cyclodextrin (alfaxalone-HPCD) was first marketed for veterinary use in Australia in 2001 and has since progressively became available throughout the world, including the USA, where in 2012 Food and Drug Administration (FDA) registration was granted. Despite the growing body of published works and increasing global availability of alfaxalone-HPCD, the accumulating evidence for its use in cats has not been thoroughly reviewed. The purpose of this review is: (1) to detail the pharmacokinetic properties of alfaxalone-HPCD in cats; (2) to assess the pharmacodynamic properties of alfaxalone-HPCD, including its cardiovascular, respiratory, central nervous system, neuromuscular, hepatic, renal, haematological, blood-biochemical, analgesic and endocrine effects; and (3) to consider the clinical application of alfaxalone-HPCD for sedation, induction and maintenance of anaesthesia in cats. Based on the published literature, alfaxalone-HPCD provides a good alternative to the existing intravenous anaesthetic options for healthy cats.

Introduction

Alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione) is a synthetic neuroactive steroid, which enhances the interaction of the inhibitory neurotransmitter gamma (γ) aminobutyric acid type A $(GABA)_A$ receptor complex to produce anaesthesia and muscle relaxation (Harrison and Simmonds, 1984; Albertson, 1992). Alfaxalone was first marketed as an anaesthetic in 1971 co-formulated with a similar, less potent, neuroactive steroid, alfadolone (3α,21-dihydroxy-5α-pregnane-11,20-dione), and dissolved in 20% W/V polyethoxylated castor oil surfactant (Cremophor EL, BASF Fine Chemicals) (Child et al., 1971).

This three-in-one formulation (CT 1341), which was marketed for both human (Althesin, GlaxoSmithKline) and veterinary (Saffan, GlaxoSmithKline) administration, caused severe side effects in numerous species. In cats the predominant adverse effects were hyperaemia and oedema of the pinnae and forepaws, urticaria and skin erythema (Dodman, 1980). CT 1341 caused an unacceptably high incidence of anaphylactoid reactions in dogs and humans, which subsequently saw Althesin withdrawn from human clinical practice in 1984 (Watt, 1975; Abraham and Davis, 2005). These adverse effects were mainly attributed to the Cremophor EL vehicle and, while Saffan continued to be available for veterinary use until 2002, it was contraindicated for use in dogs.

In 1999, a lyophilised powder of alfaxalone and cyclodextrin requiring reconstitution (Alfaxan-CD) was released; however, this product was only registered for use in cats. In 2001 a clear colourless, surfactant-free, aqueous formulation of 1% W/V alfaxalone dissolved with 2-hydroxpropyl-β-cyclodextrin (HPCD) was released for veterinary use in Australia (Alfaxan-CD RTU, Jurox) (Brewster et al., 1989; Estes et al., 1990); this new formulation has not demonstrated the side-effects observed with the previous (CT 1341) preparation (APVMA, 2010).

Cyclodextrins are ring-shaped chains of sugar molecules arranged so that their hydrophilic domains face outwards and their lipophilic domains face inwards. They are soluble in water and provide, within their hydrophobic core, space for interaction with hydrophobic molecules, such as steroids. The 1:1 molar HPCD:alfaxalone aggregate therefore behaves as one molecule to form an isotropic solution in water. This aggregate must dissociate in vivo, allowing the alfaxalone to obtain pseudo-equilibrium between its free (unbound) concentration and those molecules that are bound to plasma proteins and cell membranes (Brewster et al., 1989). The use of cyclodextrins in pharmaceutical formulations has been reviewed by Davis and Brewster (2004).

Although the newest formulation of alfaxalone (alfaxalone-HPCD) has been made available in many countries, including Australia, New Zealand, South Africa, Thailand, Canada and numerous European countries, the accumulating evidence for its use in

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cats has not been thoroughly reviewed. In September 2012, alfaxalone-HPCD was approved by the USA Food and Drug Administration (FDA)[1] for induction and maintenance of anaesthesia in dogs and cats in the United States, although its market release was delayed by the Drug Enforcement Administration's (DEA)[2] process for scheduling. Alfaxalone-HPCD provides an alternative in the face of anaesthesia drug shortages (i.e. propofol, thiopental).

The aim of this article is to review the pharmacology of alfaxalone and the clinical application of the HPBC solubilised formulation in the cat. This review was compiled from available original and retrospective studies, reviews, texts, forum proceedings and recent research in both the human and veterinary medical fields. Articles were retrieved with a combination of search engines including but not limited to PubMed, Thomas Reuters Web of Knowledge, Commonwealth Agricultural Bureau (CAB) Abstracts, and Ovid Medline. Relevant articles retrieved were reviewed and, where appropriate, their reference citations were searched for additional pertinent articles. Attempts were made to assess human and animal studies for relevance pertaining to the clinical application of alfaxalone in the cat and to make recommendations in accordance with the principles of evidence-based medicine. The resulting relative scarcity of peer reviewed literature investigating alfaxalone in the cat is worth noting. A total of three pharmacological studies, eight clinical studies, one case report and two conference proceedings were found in the literature to date.

Mechanism of anaesthetic effect

The primary mechanism of anaesthetic action of alfaxalone is attributed to positive allosteric modulation of the $GABA_A$ receptor, a ligand-gated chloride ion (Cl^-) channel receptor for the neurotransmitter GABA, which universally inhibits neuronal excitability (Harrison and Simmonds, 1984; Albertson, 1992). Alfaxalone directly binds to $GABA_A$ receptors, potentiating the effects of endogenous GABA, causing movement of Cl^- into the cell, hyperpolarisation of the neuron and inhibition of action potential propagation (Lambert et al., 2003). Investigations have also revealed a dual mechanism of action of alfaxalone. At low concentration, alfaxalone allosterically modulates the amplitude of GABA-induced ion currents, whereas, at higher concentrations, alfaxalone exerts an agonist effect, similar to barbiturates (Cottrell et al., 1987; Paul and Purdy, 1992; Lambert et al., 1995). The $GABA_A$ receptor is a pentameric transmembrane ion channel at which pharmacological properties of interacting drugs are determined by both the receptor subunit composition and by drug subunit selectivity. Within the central nervous system (CNS), neurones express numerous $GABA_A$ receptor subunit isoforms (e.g. α_1–α_6, β_1–β_3, γ_1–γ_3, δ, ε, θ, π, ρ_1–ρ_3) which determine the receptor's agonist affinity, chance of opening, conductance and other pharmacological properties (Lambert et al., 2003; Olsen and Sieghart, 2008). The variability in pharmacological properties of drugs that act at the $GABA_A$ receptor is due to variation in drug specificity for a particular subunit. The receptor subunit specificity for binding of alfaxalone has been evaluated in human recombinant $GABA_A$ receptors, and this work demonstrated that alfaxalone acts best as a positive allosteric modulator on the $\alpha_1\beta_1\gamma_2L$ receptor isoform (Maitra and Reynolds, 1998).

[1] See: New Animal Drugs; Approvals; Changes of Sponsor; Change of Sponsor's Name; Change of Sponsor's Address; Alfaxalone; Ivermectin and Clorsulon; Narasin; Triptorelin. From the Federal Register Online via the Government Printing Office [FR Doc No: 2012-N-0002] 77, pp. 64715–64718. http://www.gpo.gov/fdsys/pkg/FR-2012-10-23/html/2012-25989.htm (accessed 15 April 2014).

[2] Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV. From the Federal Register Online via the Government Printing Office [FR Doc No: 2013-06651] 78, pp. 17895–17900. http://www.gpo.gov/fdsys/pkg/FR-2013-03-25/html/2013-06651.htm (accessed 15 April 2014).

Pharmacokinetics of alfaxalone

The pharmacokinetics of alfaxalone in cats has been investigated in one study involving eight cats and was found to be nonlinear (Whittem et al., 2008). When the pharmacokinetic parameters for a drug (e.g. clearance and volume of distribution) are dose-independent, they are said to be 'linear'. This is a characteristic of first order pharmacokinetics. For drugs with linear pharmacokinetics, as the dose is increased, the plasma concentration and the area under the plasma concentration–time curve (AUC) increases in proportion to the change in dose. Linear pharmacokinetics are usually maintained when the mechanisms of a drug's clearance do not approach a maximum (i.e. they do not saturate) at concentrations usually achieved in vivo. However, clearance mechanisms become saturated for some drugs or the drug's pharmacodynamic effects may alter the drug's own distribution or clearance. For these drugs the pharmacokinetic parameters, such as clearance or volume of distribution may vary depending on the administered dose, or may vary as a function of time.

The pharmacokinetic properties of alfaxalone in cats have been demonstrated to be nonlinear. In nonlinear pharmacokinetics, the drug's effects and persistence are not predictable at different doses and the variability between individuals may be greater than expected for drugs with linear pharmacokinetic behaviour. For a single 5 mg/kg IV dose of alfaxalone, the volume of distribution was 1.8 L/kg; the mean terminal plasma elimination half-life ($t_{1/2}$) was approximately 45 min; and the mean plasma clearance was 25.1 ± 7.6 mL/kg/min, which represented approximately 5–10% of cardiac output (Whittem et al., 2008). Although the effective plasma concentration for this study was not measured, the mean of the 'average steady state' concentration of alfaxalone in the plasma was 2.8 ± 1.3 mg/L (Whittem et al., 2008). The authors concluded that, at clinical dose rates, neither alfaxalone nor its effect accumulated to a clinically relevant extent.

This large clearance of alfaxalone is suggestive of rapid metabolic clearance of the parent moiety (Whittem et al., 2008). Rapid hepatic metabolic clearance by the liver has been identified in other species as a likely mechanism of recovery from alfaxalone anaesthesia (Sear and McGivan, 1981). Renal, pulmonary and, potentially, cerebral metabolism are also speculated to be involved in the elimination of this drug (Holly et al., 1981; Nicholas et al., 1981; Sear, 1996; Celotti et al., 1997; Hiroi et al., 2001; Ferre et al., 2006). Studies in humans and rats have demonstrated that metabolites of alfaxalone are primarily excreted in the urine, with a small amount likely to be excreted in the bile (Strunin et al., 1977; Sear, 1996). Although the exact metabolic clearance and excretion mechanisms are unknown in cats, the alfaxalone metabolites produced are similar to those of humans and rats, allowing for the extrapolation that renal elimination is probably also important in this species (Warne, 2013).

Overdose and toxicity of alfaxalone

The therapeutic index is the ratio of the dose of the drug necessary to induce death in 50% of the animals to which the drug is administered (LD_{50}) relative to the dose of drug necessary to induce the desired effect in 50% of the animals to which it is administered (ED_{50}). In cats, the therapeutic index for alfaxalone has not been established; however, in mice and rats, the therapeutic index for Althesin is 30.4 and 28.7 respectively (Davis and Pearce, 1972; Hogskilde et al., 1987). The higher the therapeutic index, the safer the drug is considered to be. However the therapeutic index does not take into consideration the gradient of the concentration–response curve. A drug with a reasonable therapeutic index, but a low gradient, may have an effect in 90% of the animals to which it is administered (ED_{90}) close to the LD_{50}, decreasing the safety margin