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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caused an unacceptably high incidence of anaphylactoid reactions in dogs and humans, which subsequently saw Althesin withdrawn from human clinical practice in 1984 (Watt, 1975; Abraham and Davis, 2005).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

of the drug. Therefore, the therapeutic index is not always useful as a measure of a drug's clinical safety.

The manufacturer of alfaxalone reports acute tolerance of overdose of up to five times in the cat (up to 25 mg/kg IV); however 1/8 cats died suddenly following administration of a supraclinical dose (25 mg/kg IV) (Whittem et al., 2008). Gross pathological findings of this cat at postmortem examination revealed possible myocardial thickening of the left ventricle (7.2 mm) compared with the right ventricle (1.3 mm), although the heart weight was normal.

Pharmacodynamics

A summary of the pharmacodynamic effects of alfaxalone in the cat is provided in Table 1.

Cardiovascular effects

There have been few studies evaluating the cardiovascular effects of alfaxalone-HPCD in cats (Heit et al., 2004; Whittem et al., 2008; Muir et al., 2009; Taboada and Murison, 2010; Ramoo et al., 2013). Alfaxalone-HPCD induces a dose-dependent decrease in heart rate (HR), cardiac output (CO) and arterial blood pressure following IV administration in cats (Whittem et al., 2008; Muir et al., 2009). These effects support the titration of this anaesthetic agent whenever administered intravenously. At a clinically relevant dose (5 mg/kg IV) Muir et al. (2009) reported that alfaxalone-HPCD without concomitant medications produced mild vasodilatory changes (decreased systemic vascular resistance) and negligible changes in HR (decreased) resulting in a minimal decrease in CO. At supraclinical doses (15 and 50 mg/kg IV), these cardiovascular parameters were significantly decreased relative to pre-induction values (Muir et al., 2009).

A decrease in systolic arterial blood pressure (SBP) and HR was reported by Whittem et al. (2008), and Taboada and Murison (2010), following induction of anaesthesia at clinically relevant doses (5 and 4.7 mg/kg IV, respectively). In the study by Whittem et al. (2008), no confounding drugs were administered prior to anaesthesia; however, in the study by Taboada and Murison (2010), cats received

Table 1
Summary of the pharmacodynamic effects of alfaxalone in cats.

	Dose summary and effects	Comments	References
Dosage	Induction: 1–3 mg/kg IV (premedicated)		Zaki et al., 2009 Beths et al., 2014 Grubb et al., 2013
	4–5 mg/kg IV (unpremedicated)		
	10 mg/kg IM	IM route not recommended due to the large volume required and prolonged recoveries with excitation	
	Sedation: 2–3 mg/kg SC/IM	Efficacious when given IM; does not cause tissue irritation; however, large volume required (0.2–0.3 mL/kg)	Ramoo et al., 2013
	TIVA: 24–250 μg/kg/min IV	Adjunctive analgesic/anaesthetic agents permit dose reduction	Beths et al., 2014 Vettorato, 2013
Cardiovascular	Dose-dependent decrease in HR, CO, MAP and SVR	Cardiovascular effects are well tolerated in healthy cats	Whittem et al., 2008 Muir et al., 2009
Respiratory	Dose-dependent decrease in RR and MV similar to propofol		Taboada and Murison, 2010
	Dose-dependent increase in PIA	Decreased frequency of PIA when administered slowly to effect	Muir et al., 2009 Taboada and Murison, 2010 Beths et al., 2014
Central nervous system	Dose-dependent decrease in CBF, $CMRO_2$ and ICP	CNS effects of alfaxalone-HPCD extrapolated from CT 1341 findings	Baldy-Moulinier, Besset-Lehmann, Passouant 1975 Baldy-Moulinier and Besset-Lehmann, 1975
		Potential clinical application for neuroanaesthesia	Baldy-Moulinier and Besset-Lehmann, 1975
Neuromuscular	A centrally positioned eye is more likely to be maintained during induction compared with propofol	Eye position is unlikely to be a reliable indicator of anaesthetic depth in cats induced with alfaxalone-HPCD	Herbert and Murison, 2013
	Suitable for evaluation of laryngeal function		Nelissen et al., 2012
Hepatic and renal	No adverse effect reported		Whittem et al., 2008
Metabolism/ excretion	Metabolised via phase I and II hepatic metabolism	May be more advantageous over propofol for prolonged infusion. It is speculated that alfaxalone-HPCD is less likely to accumulate	Warne, 2013
	Metabolites primarily excreted in the urine		Strunin et al., 1977 Sear, 1996
Haematology and biochemistry	No changes reported	Heinz body formation has not been reported with alfaxalone-HPCD	Whittem et al., 2008
Analgesia	Not analgesic	Adjunctive analgesia required for painful procedures	Winter et al., 2003 Murison and Taboada, 2010
Endocrine	Does not decrease testosterone levels in male domestic cats and cheetahs	Unlike thiopentone and ketamine anaesthesia (unknown for propofol) Endocrine effects of alfaxalone-HPCD extrapolated from CT 1341 findings The effects of alfaxalone-HPCD on adrenal suppression have not been evaluated	Wildt et al., 1984 Johnstone and Bancroft, 1988
Induction/recovery	Smooth induction and recovery; however greater incidence of trembling and paddling in recovery compared with propofol	Quality of recovery improves with sedation	Zaki et al., 2009 Mathis et al., 2012
	Recovery dependent on hepatic metabolism	Hepatic insufficiency may prolong recovery	Whittem et al., 2008

TIVA, total intravenous anaesthesia; HR, heart rate; CO, cardiac output; MAP, mean arterial blood pressure; SVR, systemic vascular resistance; RR, respiratory rate; MV, minute volume; PIA, post-induction apnoea; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; ICP, intracranial pressure.

acepromazine (0.05 mg/kg IM) and meloxicam (0.3 mg/kg SC). While the administration of these drugs (primarily acepromazine) could have partially contributed to these cardiovascular findings, the extent and timing of the pharmacodynamic effects more closely resemble the pharmacokinetics of alfaxalone rather than acepromazine. The lowest mean arterial blood pressures (Taboada and Murison, 2010, 50–60 mmHg; Whittem et al., 2008, 70–90 mmHg) occurred at the first reported post-induction measurement (5 min post-induction) (Whittem et al., 2008; Taboada and Murison, 2010). In contrast, clinically relevant anaesthetic induction doses of the former CT 1341 formulation produced transient tachycardia combined with a short-lasting fall in mean arterial blood pressure (MAP) during and just after rapid induction of anaesthesia with clinically relevant doses of CT 1341, followed 2.5–5 min after the start of injection by a decrease in heart rate and persisting fall in MAP (Child et al., 1972). The fact that this study reported tachycardia and hypotension associated with induction of anaesthesia occurring within 2.5–5 min after injection, suggests that, in their studies, Muir et al. (2009), Taboada and Murison (2010) and Whittem et al. (2008) may have failed to observe the full extent of any post-induction decrease in arterial blood pressure, since recordings were not evaluated during this time period.

The increase in HR observed by Child et al. (1972) may be due to the rapid speed of induction (10–25 s) and was likely to have occurred in response to the associated post-induction hypotension. It is possible that, with rapid induction, the subsequent hypotension occurs sooner than if induction had occurred more slowly, allowing a brief baroreceptor response, prior to the onset of CNS drug concentrations, which in turn ablate the baroreceptor response. Although the baseline HR of the subjects was high (mean HRs were 193–214 beats per min), with increasing alfaxalone-HPCD induction doses (administered over 1 min), Muir et al. (2009) reported a dose-dependent decrease in HR.

The decrease in CO reported following induction of anaesthesia with alfaxalone-HPCD is likely due to a decrease in HR and stroke volume (SV). SV is determined by preload, afterload and myocardial contractility. Since preload and afterload remained relatively unchanged (indicated by mean right atrial and pulmonary arterial pressures, respectively), the most significant contributor to the decrease in SV must be reduced contractility (Muir et al., 2009). This is supported by the dose-dependent decrease in rate-pressure product (RPP) following administration of alfaxalone-HPCD (Muir et al., 2009). Rate-pressure product (HR × SBP; beats mmHg/min^{-1}) is an index of myocardial oxygen consumption and contractility.

In a study involving eight healthy adult cats, a clinically relevant anaesthetic induction dose of alfaxalone-HPCD (5 mg/kg IV) produced minimal decreases in RPP and CO relative to pre-induction values (Muir et al., 2009). At supraclinical doses of alfaxalone-HPCD (15 and 50 mg/kg IV), the same study reported a significant decrease in RPP, CO and systemic vascular resistance (SVR), suggestive of negative inotropic effects, decreased SV and vasodilatory effects. It is hypothesised that at these high doses, alfaxalone-HPCD exerts both centrally mediated and direct cardiac depressive effects. Systemic vascular resistance was maintained at clinically relevant doses of alfaxalone-HPCD (Muir et al., 2009). It must be noted that the methodology employed by Muir et al. (2009) to calculate RPP using MAP (i.e. MAP × HR) rather than SBP (i.e. SBP × HR) departed from the standard recognised formula.

Alfaxalone-HPCD has demonstrated some cardiovascular depression at clinically relevant doses in healthy cats (Whittem et al., 2008; Muir et al., 2009; Taboada and Murison, 2010). There is only one published study that compares the cardiovascular effects of alfaxalone and propofol (Taboada and Murison, 2010). This study found no significant differences in cardiovascular depression in cats when anaesthesia was induced using alfaxalone-HPCD compared with propofol. It is important to recognise that, although alfaxalone-HPCD has demonstrated minimal cardiovascular depression at clinically relevant doses, appropriate care should be taken when administering alfaxalone-HPCD to cats with cardiovascular compromise, since the depressive effects have not been investigated in this cohort and may be more significant than findings reported in healthy cats.

Respiratory effects

Alfaxalone-HPCD induces a dose-dependent decrease in respiratory rate and minute volume similar to propofol (Taboada and Murison, 2010). Several studies have not observed post-induction apnoea (PIA) when clinically relevant doses of alfaxalone-HPCD were administered IV over approximately 60 s (Whittem et al., 2008; Taboada and Murison, 2010; Beths et al., 2014). In addition, one study did not observe any PIA in eight cats administered a supraclinical dose (25 mg/kg IV over 60 s) of alfaxalone-HPCD (Whittem et al., 2008). Post-induction apnoea was defined by Whittem et al. (2008) and Beths et al. (2014) as an absence of spontaneous ventilation for a period >30 s and by Taboada and Murison (2010), as >60 s. In contrast, Zaki et al. (2009) observed a PIA of 80 s in one of 22 unpremedicated cats administered alfaxalone-HPCD 1% W/V (2.7–5.8 mg/kg IV over 60–90 s until endotracheal intubation was achieved). In the same study, there were no reports of PIA of duration greater than 15 s in premedicated cats (0.03 mg/kg acepromazine and 0.3 mg/kg butorphanol SC) given 1% alfaxalone-HPCD or 1% alfaxalone-HPCD W/V diluted with sterile water to 0.5% W/V (1.7–4.7 mg/kg IV administered over 60–90 s). Muir et al. (2009), defining apnoea as no physical evidence of breathing for a period of 20 s, observed a dose-dependent increase in the incidence of PIA, reporting 12.5, 25.0 and 100.0% in unpremedicated cats induced with alfaxalone-HPCD administered over 60 s at doses of 5.0, 15.0 and 50.0 mg/kg IV, respectively. A decrease in the frequency of PIA has been reported when alfaxalone-HPCD is administered slowly to effect (Taboada and Murison, 2010; Beths et al., 2014).

Effects on cerebral haemodynamics and metabolism

The effects of alfaxalone-HPCD on cerebral haemodynamics and metabolism are unknown; however, considering the effects of the previous alfaxalone-alfadolone formulation in both cats and humans, a dose-dependent decrease in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) is most likely to occur after the administration of alfaxalone (Baldy-Moulinier et al., 1975; Sari et al., 1976; Rasmussen et al., 1978; Bendtsen et al., 1985). When anaesthesia was maintained via a CRI of CT 1341 in cats (and arterial partial-pressure of CO_2 was kept constant) a dose-dependent decrease in CBF and intracranial pressure (ICP) was reported, as well as concurrent cerebral vasoconstriction (Baldy-Moulinier and Besset-Lehmann, 1975).

Alfaxalone is thought to exert its effects on CBF primarily via its depressant effect on intracellular neuronal metabolism, which leads to metabolically controlled secondary vasoconstriction and a corresponding decrease in CBF (Rasmussen et al., 1978). The influence of alfaxalone on ICP, cerebral haemodynamics and metabolism supports the evaluation of the application of this drug for neuroanaesthesia (Warne et al., 2014).

Neuromuscular effects

Cats anaesthetised with alfaxalone-HPCD maintain a more centrally positioned eye at the depth of anaesthesia appropriate for orotracheal intubation than those anaesthetised with propofol (Herbert and Murison, 2013). These results suggest that eye position is unlikely to be a reliable indicator of anaesthetic depth during induction in cats anaesthetised with alfaxalone-HPCD and,

as such, greater significance should be given to other variables, such as muscle tone, jaw tone, the presence or absence of reflexes (pedal withdrawal, palpebral, corneal, gag, swallow and cough) and reaction to noxious stimuli.

A study comparing three anaesthetic induction protocols (alfaxalone-HPCD, midazolam and ketamine, propofol) used to assess laryngeal function in cats ($n = 35$) found that alfaxalone-HPCD was the only protocol in which arytenoid cartilage motion was maintained in all cats evaluated (Nelissen et al., 2012). There was no significant difference in the area of the rima glottides in cats anaesthetised with alfaxalone compared with other protocols (Nelissen et al., 2012).

The CT 1341 co-formulation reduces lower oesophageal sphincter pressure without a parallel fall in gastric pressure, and thus may increase the risk of gastro-oesophageal reflux during induction of anaesthesia in cats (Hashim and Waterman, 1991). However, this effect may have been specific to the formulation and has not been evaluated with alfaxalone-HPCD.

Hepatic and renal effects

No adverse hepatic or renal effects have been associated with alfaxalone-HPCD anaesthesia in the cat. Alfaxalone is metabolised in vitro by feline and canine hepatocytes through both phase I (cytochrome P450 dependent metabolites) and phase II (glucuronide and sulphate conjugation dependent) enzymatic systems (Fig. 1) (Warne, 2013). Cats and dogs both formed the same five phase I alfaxalone metabolites (allopregnatrione, 3β-alfaxalone, 20-hydroxy-3β-alfaxalone, 20-hydroxyalfaxalone and 2α-hydroxyalfaxalone) (Warne, 2013). The phase II metabolites observed were alfaxalone glucuronide (dog and cat), 20-hydroxyalfaxalone sulphate (dog and cat), 3β-alfaxalone sulphate (cat only) and 2α-hydroxyalfaxalone glucuronide (dog only) (Warne, 2013). The major alfaxalone conjugates in the cat were 20-hydroxyalfaxalone sulphate and alfaxalone glucuronide, while in the dog the predominant conjugate was alfaxalone glucuronide (Warne, 2013).

Haematological and blood biochemistry

No changes in haematology or blood biochemistry have been associated with alfaxalone-HPCD anaesthesia in the cat (Whittem et al., 2008).

Analgesia

Murison and Taboada (2010) found no beneficial analgesic effect of alfaxalone-HPCD compared with propofol. Previous studies have shown that CT 1341 exhibits a direct depressive action on sensory synapses in dorsal horn neurones of the feline spinal cord, thereby imparting an analgesic effect (Le Bars et al., 1976). These antinociceptive effects were subsequently attributed to the interaction of the alfadolone component of the CT 1341 co-formulation and its action at $GABA_A$ receptors in the spinal cord (Harrison et al., 1987a, 1987b; Mistry and Cottrell, 1990; Nadeson and Goodchild, 2000). This was further supported by recent murine studies, which found that alfadolone caused antinociceptive effects with no signs of sedation, while alfaxalone caused sedation and anaesthesia, with no signs of antinociception (Winter et al., 2003).

Endocrine effects

The endocrine effects of alfaxalone-HPCD have not been investigated; however, CT 1341 anaesthesia does not affect testosterone levels in male domestic cats and cheetahs, in contrast to thiopentone and ketamine anaesthesia, which have been reported to reduce testosterone levels in cats (Wildt et al., 1984; Johnstone and Bancroft, 1988). It is thought that alfaxalone is highly specific for the $GABA_A$

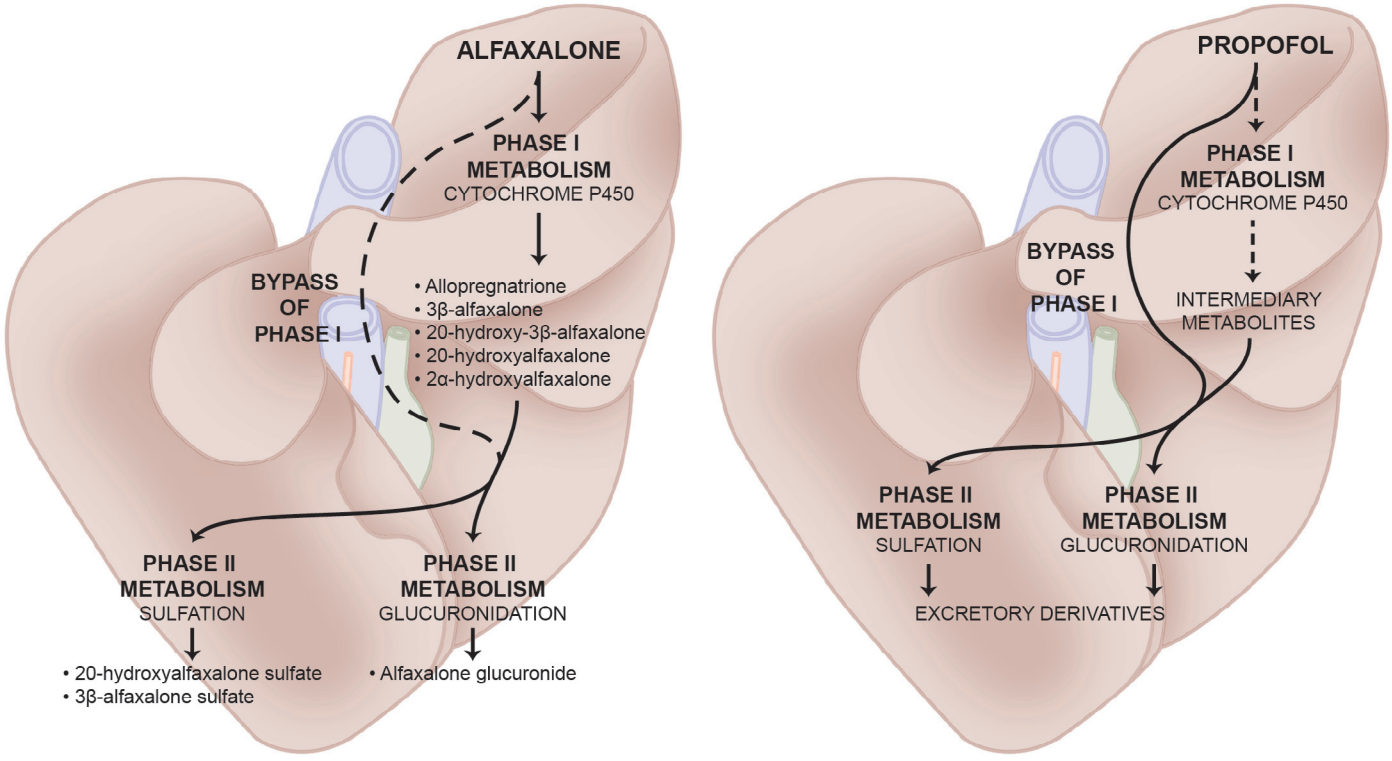

Fig. 1. Comparison of propofol and alfaxalone hepatic metabolism pathways in the cat.

receptor complex and does not interact with any of the classical cytosolic ho rmonal steroid receptors (Visser et al., 2002).

Clinical application of alaxalone

Alfaxalone-HPCD for sedation and induction of anaesthesia

Administration of alfaxalone-HPCD by the perivascular or IM routes does not cause tissue irritation (Heit et al., 2004). Alfaxalone-HPCD can be used as an effective IM or SC sedative or premedication agent in cats at 2–3 mg/kg, alone or in combination with other hypnotic or analgesic agents (Ramoo et al., 2013). The peak sedative effect occurs approximately 30–45 min after SC administration (Ramoo et al., 2013). Intramuscular administration of alfaxalone-HPCD provides induction of anaesthesia with stable cardiovascular and respiratory effects; however, this route is not recommended due to the large volume required (i.e. 10 mg/kg equating to 1 mL/kg IM) and poor, prolonged recoveries with excitement, ataxia and hyperreactivity (Grubb et al., 2013).

Anaesthetic premedication with medetomidine (20 μg/kg IM) plus morphine (0.3 mg/kg IM) reduces the alfaxalone-HPCD dose requirement for induction of anaesthesia (1.7 mg/kg IV) compared with the labelled dose for induction of anaesthesia in cats (5 mg/kg IV) (Beths et al., 2014). In another study, the premedication combination acepromazine (0.03 mg/kg SC) plus butorphanol (0.3 mg/kg SC) has also been shown to reduce the alfaxalone-HPCD dose requirement for induction of anaesthesia from 4.2 mg/kg IV (without premedication) to 3.4 mg/kg IV (with premedication). Premedication also improved the quality of recovery after alfaxalone-isoflurane anaesthesia (Zaki et al., 2009). The uses of a 0.5% W/V rather than a 1.0% W/V concentration of alfaxalone-HPCD has also been shown to further reduce the total dose required to achieve intubation to 1.9 mg/kg when combined with acepromazine/butorphanol premedication (Zaki et al., 2009). Laboratory testing performed by the manufacturer indicates that dilution in 0.9% saline does not result in degradation of alfaxalone-HPCD (S. Cumming, personal communication).

No substantial differences have been found between alfaxalone-HPCD and propofol with respect to the quality of induction and recovery; however, cats induced with alfaxalone-HPCD exhibit a greater incidence of paddling and trembling during the recovery period (Mathis et al., 2012).

Alfaxalone-HPCD for maintenance of anaesthesia in the cat

Alfaxalone-HPCD total intravenous anaesthesia (TIVA) is effective for neutering surgery in feral and domestic cats at a median rate of 180 (range 60–250) μg/kg/min IV following 20 μg/kg IM medetomidine and 0.3 mg/kg IM morphine premedication and alfaxalone-HPCD IV induction (Beths et al., 2014). Alfaxalone-HPCD TIVA has also been used successfully for neutering procedures in kittens less than 12 weeks of age, with no reported side-effects (O'Hagan et al., 2012). Alfaxalone-HPCD based TIVA has been reported for prolonged anaesthetic maintenance (450 min) of a 14-year-old male domestic cat undergoing exploratory sternotomy and diaphragmatic hernia repair (Vettorato, 2013). The median infusion rate of alfaxalone-HPCD was 79 (range 24–121) μg/kg/min; adjunctive perioperative analgesia consisted of methadone 0.2 mg/kg IM (prior to anaesthesia) and remifentanil 0.3–0.45 μg/kg/min IV throughout the procedure (Vettorato, 2013). Cardiovascular stability and a relatively short and smooth recovery were reported, with spontaneous ventilation and tracheal extubation occurring 30 and 60 min after alfaxalone suspension, respectively (Vettorato, 2013). Alfaxalone-HPCD appears to be a good alternative to propofol for maintenance of anaesthesia.

Comparison of alfaxalone-HPCD and propofol for multiple or prolonged anaesthesia in the cat

Beths (2008) found that propofol elimination in domestic cats is almost exclusively via phase II hepatic metabolism, involving both glucuronide and sulphate conjugation pathways (see Appendix A: Supplementary Fig. S1). Delayed recoveries seen in cats following prolonged propofol anaesthesia (Pascoe et al., 2006) may be attributed to the relative deficiency of glucuronidation in cats (Fig. 1). This deficiency means there is a greater reliance on the slower and more easily saturated sulphate conjugation pathway (Jordan and Woolf, 1987). The relative deficiency of glucuronidation in cats explains this species sensitivity to phenolic compounds (e.g. paracetamol/acetaminophen) (Court and Greenblatt, 2000) and can explain the lower propofol hepatic clearance (8.6 mL/kg/min) compared with alfaxalone (25.1 mL/kg/min) (Whittem et al., 2008; Bester, 2009). The high alfaxalone clearance is also suggestive of hepatic blood flow dependence for metabolism and possible extrahepatic metabolism (Whittem et al., 2008).

Nonlinear pharmacokinetics have been described when consecutive maintenance doses of alfaxalone-HPCD (2 mg/kg every 7 min) were administered to healthy cats (Whittem et al., 2008). In the presence of hepatic disease, the pharmacokinetics of alfaxalone might change and prolonged infusion might result in accumulation. Few studies evaluating prolonged alfaxalone-HPCD infusion in the cat exist in the literature; however a recent case report described maintenance of alfaxalone-HPCD anaesthesia in a 14-year-old male neutered cat for 7.5 h (Vettorato, 2013). Anaesthesia was cardiovascularly stable throughout and recovery was smooth. Spontaneous ventilation and tracheal extubation were recorded 30 and 60 min after alfaxalone-HPCD suspension, respectively.

'Shelf life' of alfaxalone-HPCD

Alfaxalone in HPBC does not support log-phase growth of several bacterial genera (Bar and Ulitzur, 1994); however, nor does it eliminate contamination in the alfaxalone formulation (Strachan et al., 2008). Shelf life is determined by the need for both chemical and microbiological (broached vial) stability. Although alfaxalone in HPBC is stable chemically, restrictions in shelf-life exist because the formulation does not contain a microbiocidal preservative and does not kill bacteria. Different countries set different criteria for broached vial stability after microbial contamination. In the UK, labelled recommendations are that any solution remaining in the vial following withdrawal of the required dose should be discarded. In Australia and New Zealand, the labelled recommendations state that the contents of broached vials should preferably be used within 24 h, but may be stored if necessary at 4 °C for up to 7 days, provided contamination is avoided. In North America, the manufacturer advises that any unused product should be discarded within 6 h.

Conclusions

Alfaxalone-HPCD is an effective CNS depressant agent, which has demonstrated minimal impact on the cardiovascular and respiratory system in healthy cats. Taking into consideration the very low incidence of adverse drug related events reported, the newest formulation of alfaxalone provides a good alternative to the existing intravenous anaesthetic options for healthy cats, although further work is required to fully understand the pharmacology in this species. On the basis of known pharmacological properties, and clinical and experimental reports, alfaxalone-HPCD could be suitable for TIVA, although further in vivo studies are needed to confirm its application for multiple or prolonged anaesthesia in cats.

Conflict of interest statement

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.tvjl.2014.12.011.

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