

# New Drugs in Anesthesia

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## NEWER ANESTHETICS

Etomidate and propofol are two recently introduced injectable monoanesthetics that have gained wide use in human anesthesia and in some veterinary teaching hospitals. Most recent veterinary medicine graduates have knowledge and experience with these two drugs through their formal anesthesia training. Etomidate is a carboxylated imidazole with GABA-like effects on the central nervous system, similar to the barbiturates. Propofol (Diprivan) is a substituted isopropylphenol, formulated as a 1% aqueous emulsion containing 10% soybean oil, 1.2% egg lecithin, and 2.25% glycerol.

### Clinical Use

Etomidate undergoes rapid hepatic metabolism, resulting in rapid recovery following long-term infusion. This makes etomidate an ideal outpatient injectable anesthetic. It induces minimal cardiovascular and respiratory depression. Etomidate has a wide margin of safety with a therapeutic index of 16 in the dog. The therapeutic index for thiopental is 7. When used alone in dogs, at doses sufficient to produce anesthesia (up to 3 mg/kg IV), heart rate, pressure, and contractility are not depressed. Etomidate may be the superior agent for C-section surgery as offspring have a shorter time to sustained respiration when compared to an equidepressant dose of thiopental. Etomidate decreases  $CMRO_2$  and has anticonvulsant properties that may be brain protective. Temporary inhibition of steroidogenesis in man and dogs has been reported. The lack of stress response to surgery appears to have minimal or no deleterious effects on patient outcome. If concern is present, the adverse effects on adrenal function can be overcome by the administration of cortisol. The use of etomidate for induction only or as a single bolus anesthetic minimizes the effects of this action. Prolonged sedation or anesthesia with etomidate infusions have been associated with increased morbidity and mortality in humans. Etomidate is costly, which argues against its routine use in veterinary medicine. When faced with an animal with cardiovascular instability, cirrhosis, intracranial lesions, anaphylactoid tendencies, or cesarian section, one should consider etomidate as a safe short-acting induction anesthetic.<sup>1</sup>

Propofol is as rapid acting as thiamylal. Inductions are smooth and excitement free. Recoveries are very smooth and rapid. Recovery is more rapid than from isoflurane anesthesia. Rapidity of recovery is due to propofol's rapid metabolism. In cats, a smaller total dose/duration of effect has been reported and may be due to differences in metabolism of the phenol in this species.<sup>3</sup> Recoveries in cats can be prolonged following infusions in excess of 30 minutes. Propofol can be used with single bolus technique in cats for short procedures such as castrations, ear flushes, ultrasound biopsies, and laceration repairs. The rapid smooth recovery, as with etomidate, makes propofol an ideal, although expensive, outpatient anesthetic.

When used as an induction agent, the calculated dose of propofol is approximately 6 mg/kg. In healthy patients, 25% of the calculated dose is given every 30 seconds until intubation is possible. Following induction, the anesthetic period ranges from 3 to 9 minutes, depending on the total dose required to achieve intubation. Anesthesia can be maintained with propofol by repeat bolus administration or by constant infusion. A dose of approximately 0.4 mg/kg/min delivered via a constant infusion maintains surgical anesthesia. If anesthesia is inadequate, a small bolus dose (1 mg/kg) can be given IV and the infusion rate increased 25%. If the patient is too deep, the infusion can be stopped until the patient lightens and the infusion is restarted at a lower rate (25% reduction usually). For sedation alone, a 0.1 mg/kg/min rate is useful.<sup>2</sup>

Cardiovascular depression with propofol is similar to the ultrashort-acting barbiturates. Direct myocardial depression, peripheral vasodilation, and venodilation have been reported which results in minimal hypotension. Caution should be used in dogs and cats with known hypotension or myocardial dysfunction. Apnea is common with bolus administration but can be managed as with the short-acting barbiturates.<sup>2</sup>

Propofol has been shown to be a safe anesthetic in sight hounds and emaciated patients because duration of action is not dependent on redistribution into body tissues. Induction with propofol in an average 20-lb dog is \$4.95. For this reason, propofol must be used selectively in small patients requiring short periods of anesthesia and rapid recovery.

### **Inhalation Agents**

It has become increasingly difficult to produce a better and more potent inhaled anesthetic. In many ways isoflurane is fairly close to an ideal anesthetic. What properties must a new inhalant possess? It should have the properties currently available in isoflurane: stability, nonflammability, rapid action, nonarrhythmogenicity, excellent muscle relaxation, no toxicity, no biodegradation. Secondly, it must have some additional desirable properties. New agents will continue to be halogenated but exclusively with fluorine. This will produce less potent and more volatile inhalants but will result in lower solubility and better stability. New inhalants will likely be ethers because they are less arrhythmogenic than the alkanes (e.g., halothane).

Sevoflurane is a fluorinated methyl-isopropyl ether with a blood/gas coefficient half that of isoflurane. It is more rapid acting than isoflurane resulting in faster inductions and recovery. Sevoflurane has a MAC ranging from 1.7 to 2.7 and is a cardiorespiratory depressant. Cardiovascular effects are less pronounced than those seen with equivalent

doses of isoflurane. Sevoflurane is unstable in soda lime and like other halogenated anesthetics may cause malignant hyperthermia.

Desflurane is a fluorinated methyl-ethyl ether identical in structure to isoflurane except for substitution of fluorine for the chlorine on the alpha methyl carbon. Its vapour pressure nearly equals one atmosphere at room temperature, requiring new vaporizer technology. Unlike sevoflurane, desflurane is stable in soda lime. It has the lowest blood/gas partition coefficient of all inhalants including sevoflurane. Consequently, it is the fastest acting agent and recoveries are extremely rapid. Desflurane is less potent than other halogenated agents. Its MAC varies from a low of 5.7% in rats to 10% in pigs with the dog being reported at 7.2%. Desflurane produces cardiovascular depression similar to isoflurane but is less arrhythmogenic than isoflurane.

### **Anesthetic Adjuncts**

Midazolam (Versed®) is a new water-soluble benzodiazepine. Midazolam has a short duration of action, with a rapid elimination half-life and a total body clearance. In man, midazolam has been used as a primary induction agent, as a sedative-hypnotic in subanesthetic doses, and as either of these in combination with opioids.<sup>2</sup> In healthy dogs and cats, unlike man, IV or IM administration does not induce anesthesia. Most often it is best utilized as an adjunctive agent to provide muscle relaxation in combination with ketamine, thiobarbiturates, or an opioid such as oxymorphone. The usual dose is 0.1 to 0.2 mg/kg given either IV or IM. Midazolam is rapidly absorbed following IM injection and is relatively nonpainful when compared to ketamine or diazepam IM injections. Cats will often exhibit abnormal behaviour following midazolam injection. These actions can vary from restlessness to belligerence and vocalization. It has also been associated with increased food consumption in this species. Midazolam is a good adjunctive agent for use with oxymorphone or fentanyl to maintain light anesthesia in dogs.<sup>2</sup>

Medetomidine is not yet available for clinical use in the U.S. Although it is a more selective and potent alpha 2-adrenoceptor agonist than xylazine, its pharmacologic actions are quite similar. Medetomidine induces dose-dependent anesthetic actions in both dogs and cats. The optimal clinical IM dose for minor surgical procedures seems to be 30 to 40 µg/kg in dogs and 80 to 110 µg/kg in the cat. Bradycardia is common, and vomiting and occasional muscle jerking have been reported. Medetomidine/ketamine combinations are often used to induce short periods of anesthesia and immobilization in dogs, cats, and many laboratory and zoo animal species. Medetomidine and opioid coadministration (e.g., butorphanol), will enhance sedation and analgesia beyond that achieved with either agent alone.<sup>4</sup>

### **Reversal Agents**

Flumazenil (Mazicon®) is a newly developed antagonist with weak agonist and inverse agonist activity at benzodiazepine receptors in the CNS. It has recently been released in the United States for use in humans. The recommended dose of flumazenil to acutely reverse the effects of a 10X preanesthetic overdose of diazepam (2 mg/kg) was 0.075 mg/kg.<sup>5</sup> This calculates to a 25 to 1 ratio of BNZ agonist to antagonist in the dog. Similar results were obtained following a 10X preanesthetic overdose (1 mg/kg) of

midazolam in dogs.<sup>5</sup> Flumazenil may be most helpful in reversing the prolonged sedative action of zolazepam in the cat. Zolazepam and tiletamine are combined in the product Telazol in equal parts by weight. The recommended dose is 9.7 to 15.8 mg/kg IM or SC. This dose of Telazol in cats often results in prolonged recoveries associated with slow zolazepam metabolism in this species. The availability of flumazenil makes Telazol a more reliable combination inasmuch as recovery time can be controlled by the reversal of zolazepam with flumazenil.

### **Opioid Antagonism**

The most widely used antagonists in veterinary medicine today are the opioid antagonists. Naloxone (0.04 mg/kg IM, IV, SC) is perhaps the best known and most widely used opioid antagonist. It can antagonize the actions of all opioid agonists as well as all agonist-antagonists. It is given to decrease opioid-induced CNS/respiratory depression. In this regard, naloxone should be carefully titrated to effect. Since naloxone is a competitive inhibitor at all opioid receptor subtypes (i.e., mu, kappa, sigma), once the opioid agonist is reversed and the animal appears painful, additional opioid can be administered to enhance analgesia but this practice is problematic. In contrast to naloxone, the opioid agonist-antagonists do not have strong affinity for all opioid receptor subtypes and possess varying degrees of intrinsic activity (efficacy) at the various receptors. Pentazocine, nalbuphine, butorphanol, and buprenorphine have all been used to reverse potent opioids such as morphine and oxymorphone. Of these agents, the most useful opioid antagonist for use in veterinary medicine is butorphanol. It has proven quite efficacious in reversing the sedative and respiratory depressant effects of oxymorphone and morphine in dogs while still maintaining a degree of analgesia.<sup>6</sup> In this way, the opioid agonist-antagonists provide an alternative approach to naloxone titration reversal that is not associated with complete receptor blockade and loss of analgesia.<sup>7</sup>

### **Alpha<sub>2</sub> Antagonism**

The alpha<sub>2</sub>-receptor antagonists in clinical use today include yohimbine, tolazoline, idazoxan, and atipamezole. Of these, only yohimbine is approved for veterinary use in the United States. Yohimbine, an indole alkaloid derivative, has a selectivity ratio of 60:1 for alpha<sub>2</sub>- to alpha<sub>1</sub>-receptors. Tolazoline is a mixed alpha<sub>2</sub>-alpha<sub>1</sub> antagonist with less alpha<sub>2</sub>-selectivity than is shown by yohimbine. Although yohimbine is a more specific alpha<sub>2</sub>-antagonist than is tolazoline, the latter is a more effective alpha<sub>2</sub>-antagonist in ruminants. This gives rise to interesting query on the role of alpha<sub>1</sub>- versus alpha<sub>2</sub>-adrenoreceptors as they influence sedation and analgesia in various species (e.g., cattle versus swine).<sup>8</sup>

Alpha<sub>2</sub>-antagonists rapidly and effectively reverse sedation induced by many anesthetic regimens that include an alpha<sub>2</sub>-agonist. This reflects perhaps a decreased requirement of the primary anesthetic (e.g., barbiturate when combined with xylazine) as well as the complete antagonism of alpha<sub>2</sub>-mediated sedation. Under many circumstances, a central stimulant (e.g., doxapram) can safely and effectively enhance the antagonistic action of specific alpha<sub>2</sub>-antagonists. This is particularly true when using yohimbine in ruminants. However, the alpha<sub>2</sub>-antagonists do not effectively reverse sedation or anesthesia induced

by other classes of anesthetics. For example, tolazoline was shown to have no effect on anesthesia induced by tiletamine and zolazepam.

Administration of an  $\alpha_2$ -antagonist for the reversal of  $\alpha_2$ -mediated sedation is not completely without risk. Some animals have died following the rapid intravenous injection of high doses of yohimbine and tolazoline. Hypotension and tachycardia frequently occur following rapid intravenous injection. However, clinical experience indicates that unfavourable reactions to  $\alpha_2$ -antagonists, when administered slowly by the intravenous route and in appropriate doses, are extremely rare in healthy animals. It would seem that development of  $\alpha_2$ -antagonists with greater receptor selectivity (e.g., atipamezole) would further decrease the likelihood of untoward hemodynamic reactions.

Many questions remain to be answered before the potential clinical value of  $\alpha_2$ -antagonist for reversal of CNS depression in veterinary practice is fully realized. For example, are there species differences in the undesirable responses elicited by specific  $\alpha_2$ -antagonists? It is well documented that ruminants are 20 to 30 times more sensitive to the depressant actions of xylazine than are swine. What are the implications of variation in species sensitivity to  $\alpha_2$ -agonists with regard to the pharmacodynamic profile of each  $\alpha_2$ -antagonist? Does tolazoline, with less selectivity for  $\alpha_2$ -adrenoreceptors, have a more desirable pharmacodynamic profile for functional antagonism of mixed agonists (e.g., xylazine)? Clinical experience would suggest that this is true in some species. Clinically tolazoline appear to be more effective than yohimbine in reversing xylazine-induced sedation in ruminants.

Our clinical experiences, as well as a number of scientific reports, suggest that  $\alpha_2$ -agonists reliably induce dose-dependent sedation and analgesia in numerous mammalian species. These effects can be safely enhanced by opioids or benzodiazepines. Recent studies have demonstrated that low doses of xylazine, butorphanol, and midazolam induce strong sedation, analgesia, and muscle relaxation that may be best described as light balanced anesthesia. Combining classes of drugs that activate specific but separate populations of CNS receptors (i.e.,  $\alpha_2$ , opioid, and benzodiazepine) can clearly induce synergistic anesthetic actions. This observation is of importance because each of these classes of drugs can be antagonized with a specific antagonist (e.g., atipamezole, naloxone, flumazenil). Reversal of synergistic receptor-mediated analgesia, sedation, and muscle relaxation will likely play an increasingly important role in anesthesia. Accordingly, the continued development and refinement of anesthetic techniques employing receptor-specific agonists and their antagonists ensures a future role for these classes of agents in veterinary anesthesia.<sup>8</sup>

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