Midazolam

- Premedicant for general anesthesia

Midazolam is a benzodiazepine tranquilizer that can be used for sedation and as an adjunct to general anesthesia in animals.

**PHARMACOLOGY**

Benzodiazepines have several pharmacologic effects, including mild sedation, anxiolysis, anticonvulsant activity, skeletal muscle relaxation, and anterograde amnesia. These effects are believed to result from facilitation of the actions of γ-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter in the central nervous system. Benzodiazepines bind to a specific site on the GABA<sub>₆</sub> receptor, which increases the affinity of the receptor for GABA and enhances the opening of chloride-gated channels, resulting in increased chloride conductance, cell hyperpolarization, and increased resistance to neuronal excitation.

Midazolam is a water-soluble imidazole benzodiazepine derivative. It is unique in having an imidazole ring structure that is open at low pH but closed at high pH. The commercial preparations of midazolam are buffered to an acidic pH of 3.2 to 3.5, thereby allowing midazolam to maintain its open-ring structure and water solubility. When exposed to physiologic pH in vivo following injection, the imidazole ring closes, converting midazolam into a highly lipid-soluble molecule. Because of its water solubility, midazolam does not need to be dissolved in propylene glycol, as is the case with diazepam.

Midazolam was the first benzodiazepine that could be reliably used by either IV or IM routes of administration, making it more versatile and more useful than diazepam. As a result of these unique properties, midazolam is primarily used as a premedicant for general anesthesia.

When used alone, midazolam does not provide reliable sedation in animals. Its affinity for the benzodiazepine receptor compared with diazepam is two to three times as potent, and has a more rapid onset and shorter duration of action. It is rapidly absorbed following IM injection in dogs, reaching peak plasma levels within 15 minutes with nearly complete absorption (>90% bioavailability). It is highly protein bound (>96%) and has a large volume of distribution (>3 L/kg) because of its high degree of lipid solubility. Pharmacokinetic studies have found midazolam to be rapidly metabolized, resulting in a short elimination half-life (77 minutes in dogs) and rapid clearance when compared with diazepam.

Midazolam is metabolized in the liver to active metabolites, although these compounds do not contribute to the clinical activity of midazolam because of their lower potency and shorter elimination half-lives. Metabolites are eliminated in both urine and bile. In humans, age-related alterations in liver blood flow and enzyme function have been associated with a prolonged elimination half-life of midazolam, but these findings have not been documented in animals.

**INDICATIONS**

In animals, midazolam is primarily used as a premedicant for general anesthesia. It can provide preoperative sedation and anxiolysis, improve skeletal muscle relaxation, and decrease required doses of more potent anesthetic agents needed for induction and maintenance of anesthesia.

**Sedation**

When used alone, midazolam does not provide reliable sedation in ani-
mals. Responses vary among species, and even within species there can be marked individual variation. Animals typically respond in one of two ways: They may become sedated, atactic, and attain sternal or lateral recumbency; or they may become dysphoric, excited, and resist restraint. The latter effects are more frequent following IV administration of midazolam alone and are also more commonly observed in cats than in dogs.

Midazolam can, however, be used in combination with other sedatives to obtain more predictable results. The agent can be combined with opioids to provide sedation in debilitated or critically ill patients. Sedation is typically less profound and is of shorter duration than a combination of an opioid with acepromazine; however, adverse cardiopulmonary effects of the midazolam combinations are less profound.

Midazolam can be combined with ketamine for IM administration, resulting in rapid and predictable sedation. Midazolam is also effective in decreasing salivation, seizure activity, and muscle rigidity often associated with the use of dissociative agents such as ketamine.

**Anesthesia Induction and Maintenance**

Benzodiazepines have been found to enhance the effects of other induction and maintenance anesthetic agents. The enhanced effects of benzodiazepines and barbiturates (and likely propofol and etomidate) are believed to be due to synergistic actions at the level of the GABA<sub>A</sub> receptor complex. Prior administration of IV midazolam has been found to reduce the induction dose of thiamylal by up to 18% without affecting measured cardiopulmonary parameters.

Midazolam can also be used in combination with ketamine for induction of anesthesia in dogs and cats to permit intubation of the patient. When comparing ketamine–diazepam with ketamine–midazolam in dogs, researchers found that inductions were of similar quality but that ketamine–midazolam was better overall because fewer patients required redosing to complete endotracheal intubation. Cardiopulmonary effects of both combinations are comparable, and recovery times have been found to be similar or shorter with ketamine–midazolam.

As is the case with all benzodiazepines, midazolam is effective in decreasing anesthetic requirements for inhalant anesthetics in a dose-dependent manner.

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**Anticonvulsant**

Similar to diazepam, midazolam can be used as an anticonvulsant in cases of status epilepticus. Although it is most commonly used IV because of its rapid and complete absorption, it has also been used IM in humans for this purpose.

**CAUTIONS**

Although benzodiazepines usually cause minimal or no adverse cardiopulmonary effects when used alone, when used in combination with other agents this may not always be the case. Depending on which agents are also used, cardiopulmonary responses can be variable.

Ketamine–midazolam combinations typically result in increases in heart rate and blood pressure because of the sympathomimetic effects of ketamine. However, if administered after opioid (e.g., butorphanol, oxydorphan) premedication, the cardiovascular effects of this combination are blunted. Ketamine–midazolam combinations should be used with caution to supplement isoflurane anesthesia because decreased heart rate, blood pressure, and cardiac output have been found. These responses are likely due to isoflurane blocking the cardiosupratory effects of the ketamine. In this case, a relative overdose of inhalant anesthetic may occur; therefore, vaporizer settings should be adjusted as needed to minimize adverse cardiovascular depression.

In dogs, midazolam–opioid combinations cause less cardiovascular depression than do acepromazine–opioid combinations, but respiratory depression can potentially be greater. In cats, midazolam–butorphanol administered during isoflurane anesthesia results in decreased heart rate and blood pressure and increased respiratory depression.

As with the use of any drug during general anesthesia, patients should be assessed for cardiopulmonary stability before use. Drug doses and routes of administration should also be taken into consideration, and patients should be monitored for adverse effects and supported as necessary.

**ACUTE TOXICITY**

Benzodiazepines are relatively safe anesthetic agents. Midazolam has been evaluated in dogs at 10 times its normal dose, with ataxia, barking, and behavioral arousal being the most common side effects. Flumazenil, a specific antagonist, has been developed to treat acute benzodiazepine toxicity and completely reverse any undesirable prolonged clinical effects. Flumazenil is a potent...
competitive inhibitor of benzodiazepines, binding at the GABA$_A$ receptor complex. Doses of approximately 0.05 mg/kg (13:1 agonist: antagonist ratio) IV have been found to completely reverse the effects of midazolam.\textsuperscript{7,10}

**DRUG INTERACTIONS**

Midazolam is compatible with 5% dextrose in water, 0.9% saline, and lactated Ringer’s solution and is physicochemically compatible in solution with opioids, ketamine, and anticholinergic drugs.\textsuperscript{1,3,5,18}

Because of its high degree of protein binding, there is potential to develop competitive binding with other highly protein-bound drugs such as barbiturates.\textsuperscript{4} Hepatic clearance of midazolam can be potentially decreased by hepatic enzyme inhibitors such as erythromycin and calcium-channel blockers.\textsuperscript{1}

**DOSEAGE AND ADMINISTRATION**

In dogs, midazolam has been most effective when used in the dose range of 0.1 to 0.3 mg/kg. At doses less than 0.1 mg/kg, the drug is ineffective in lowering the requirement for induction doses of thiamyl in dogs.\textsuperscript{6,7} In cats, an effective range of 0.05 to 0.5 mg/kg has been established, with a dose of 0.3 mg/kg being the most effective in combination with ketamine to allow intubation.\textsuperscript{9,19}

Because of its unique pharmacology, midazolam can be administered by IV, IM, or SC routes. The lower end of the dose range is typically for IV administration. Midazolam has also been evaluated for oral and intranasal use in dogs,\textsuperscript{2,10} but these routes have not found a clinical use to date.

For IV inductions, midazolam can be used similarly to diazepam in combination with ketamine as a 50:50 mixture (volume:volume) at a dose of 1.0 ml/9.1 kg (1.0 ml/20 lb).\textsuperscript{11} This results in a dose of 0.28 mg/kg midazolam and 5.5 mg/kg ketamine to be administered to clinical effect.

**PREPARATIONS**

Midazolam hydrochloride (Versed, Roche Laboratories) is available as 1- and 5-mg/ml solutions for injection. Generic formulations are also available.

**STORAGE AND HANDLING**

Midazolam should be stored at a controlled temperature of 15°C to 30°C and should be protected from light. When using a multidose vial, any unused portion should be discarded 28 days after the initial puncture.

**REFERENCES**