Midazolam is the newest benzodiazepine, possessing anxiolytic, sedative, amnesic, muscle relaxant and anticonvulsant properties similar to other benzodiazepine compounds. It has several important advantages over the currently available agents in this classification. The author reviews the literature on midazolam with emphasis on the pharmacodynamics and pharmacokinetics. Application of midazolam to clinical anesthesia practice is examined along with potential drug interactions.

Midazolam (Versed®) was synthesized in the United States in the mid 1970s during a search for a water soluble 1,4-benzodiazepine derivative that would satisfy the following criteria: (1) good water solubility; (2) rapid onset of action; (3) stability in solution; (4) compatibility with intravenous solutions; and (5) absence of pain on injection, erythema or thrombophlebitis. It has undergone more than 100 investigations on nearly 3000 adult patients during phase 3 clinical testing. Midazolam was approved for clinical use by the U.S. Food and Drug Administration (FDA) in 1986.

Chemistry and structure

Midazolam differs from other benzodiazepines in that it contains a fusible imidazole ring (Figure 1) that accounts for its basicity, stability in aqueous solution, and short duration of action. It causes little if any local irritation after intravenous or intramuscular injection. The parenteral preparation of midazolam is buffered to an acidic pH below 4. At physiological pH (7.4) and temperature (37°C) it becomes highly lipophilic, which results in its rapid entry into brain tissue after intravenous administration. The degree of plasma protein binding in healthy subjects averages 96-97%, which is similar to other benzodiazepines.

Pharmacodynamics

As a highly lipophilic compound, midazolam readily crosses the blood-brain barrier and produces central nervous system (CNS) effects. Midazolam appears to act at specific benzodiaz-
epine receptors in the brain with an affinity twice as great as diazepam. The hypnotic effect of midazolam appears to be related to an accumulation of the neuro inhibitory substance gamma-aminobutyric acid (GABA), plus GABA occupation of the benzodiazepine receptors. Benzodiazepines exert anxiolytic effects by increasing the glycine inhibitory neurotransmitter, and it is assumed that midazolam also exerts this type of action. Other central nervous system effects of midazolam include anticonvulsant action, muscle relaxant properties and amnesia.

Midazolam's hemodynamic effects have been investigated in normal subjects and in patients with ischemic heart disease. Hemodynamic changes that have been reported include: no change or an increase in heart rate; a decrease in mean arterial pressure (MAP), systemic vascular resistance (SVR) and left ventricular pressure (LVP); no change in peripheral vascular resistance (PVR), right ventricular pressure (RVP) or cardiac index (CI); and no change or decrease in stroke volume (SV) or rate of rise of the left ventricular pressure (dP/dt).

The hemodynamic effects of midazolam in healthy patients are limited to a small (16-18%) decrease in MAP with all other parameters maintained near normal. When testing midazolam in human subjects with ischemic heart disease, Reves, et al. concluded that the hemodynamic changes of midazolam and diazepam were not of clinical significance, and that midazolam was similar to diazepam except for a statistically significant decrease in blood pressure four to five minutes after administration of midazolam.

The mechanism for the cardiovascular effects of midazolam involves both a direct decrease in myocardial contractility and in reflex activity. A fall in blood pressure initiates the baroreflex response, simultaneously increasing heart rate and contractility with increased shunting of blood volumes into the central circulation. Patients with reduced blood volumes may therefore elicit exaggerated decreases in blood pressure in response to midazolam when compared to the normal or well compensated cardiac patient.

Midazolam appears to affect the respiratory system by central depression. The ventilatory response and the mouth occlusion pressure response to CO₂ are both depressed in normal subjects after a dose of midazolam 0.15 mg/kg. The slope of the ventilatory response curve to CO₂ is flatter than normal. These effects are very similar to those produced by diazepam 0.9 mg/kg. Patients with chronic obstructive pulmonary disease (COPD) may elicit a more rapid respiratory response to midazolam and take longer to return to baseline than normal patients.

Apnea has occurred following the administration of midazolam and is probably related to speed of injection and dose. The incidence of apnea has been reported to vary between 18 and 78%. In comparative studies, apnea occurred less often and was of shorter duration after midazolam than after thiopental.

**Pharmacokinetics**

Midazolam differs significantly from other available benzodiazepines in its pharmacokinetic profile. (See Table I for a comparison of midazolam and diazepam). The major differences include a

| Table I: Comparative pharmacokinetics: Midazolam vs. Diazepam |
|-----------------|-----------------|
| **Midazolam**   | **Diazepam**    |
| t 1/2* (min)*   | 7.2 ± 1.6       | 30-60 |
| t1/2* (hrs.)*** | 2.52 ± 0.2      | 24-57 |
| Vd (l/kg)****   | 1.72 ± 0.05     | 1.1 ± 0.3 |
| Cl (ml/min/kg)***** | 8.10 ± 0.52 | 0.38 ± 0.06 |

*Alpha elimination half life (minutes)  
**Beta elimination half life (hours)  
***Volume of distribution (liters/kg)  
****Clearance (milliliters/minute⁻¹/kg⁻¹)
distribution half-life of midazolam that is at least one-half that of diazepam and an elimination half-life of midazolam that is about ten times less than diazepam. The total body clearance of midazolam is much higher than that of diazepam. All of these factors account for the short duration of action seen with midazolam.

The termination of action occurs by extensive distribution in peripheral tissues and rapid hepatic clearance. Once distribution equilibrium is achieved, elimination of midazolam proceeds with a half-life of approximately two hours.15

Biotransformation of midazolam in humans involves hydroxylation by hepatic microsomal oxidative mechanisms. The principal metabolite is 1-hydroxymidazolam.16 Smaller amounts of 4-hydroxymidazolam are formed and even smaller amounts of 1, 4-dihydroxymidazolam can be found. (See Figure 2). These metabolites are excreted in the urine in the form of glucuronide conjugates with very little intact drug detected in the urine. The clinical effect of the pharmacological activity of the 1- and 4-hydroxymidazolam has not been established. Generally though, almost no measurable drug remains in the circulation five to six hours after a single dose.14

Several other factors influence the pharmacokinetics of midazolam, including age, gender and weight.5 The volume of distribution increases significantly in the morbidly obese patient due to the distribution of midazolam into a peripheral compartment. The nurse anesthetist should realize that there is a decrease in the elimination half life and clearance in the geriatric patient. Greenblatt et al. have shown that the elimination half life and clearance of midazolam in the elderly male is significantly decreased. Elderly patients require less midazolam on a mg/kg basis; this may be due to pharmacokinetics or to a change in sensitivity at the level of the central nervous system.5

Anesthetic uses

Induction. Midazolam has been investigated as an induction agent in anesthesia and compared to thiopental and diazepam for this use. Induction is considered complete when there is unresponsiveness to command and loss of eyelash reflex. This requires a dose of 0.2 mg/kg14 with a range between 0.1 mg/kg and 0.4 mg/kg. The induction dose of midazolam is influenced by a variety of factors including age, narcotic premedication, physical status, dose, speed of injection and serum albumin concentration.

The induction time for midazolam was about twice as long as that for thiopental.14 Apnea was less common and of shorter duration with midazolam. Recovery from midazolam was slower with greater amnesia than with thiopental. Midazolam is about 20 times more potent than thiopental.14

The onset of induction was more rapid with midazolam than with diazepam,20 and was associated with significantly less pain on injection. Midazolam is about one and one-half to two times more potent than diazepam.20 Patient acceptance was good in both studies.

Induction of anesthesia with midazolam has been investigated in patients with pre-existing illnesses such as ischemic heart disease, intracranial masses, COPD and chronic renal failure. Overall findings are favorable and midazolam may serve as a valuable alternative to thiopental in seriously ill patients.51

Maintenance. Midazolam has been studied for usefulness as a hypnotic-amnesic during maintenance of general anesthesia.22 Midazolam proved superior to thiopental because fewer adjunctive agents were required to maintain acceptable depths of anesthesia and stable hemodynamic parameters. Amnesia was better with midazolam and patients and anesthetists alike rated it better than thiopental. Midazolam can be used safely and effectively with potent inhalation agents or as an adjunct to a nitrous oxide/narcotic anesthetic.

Preoperative medication. Midazolam can be administered as a preoperative medication by mouth, intramuscularly or intravenously and will provide satisfactory hypnotic and anxiolytic results. The effects are dose-related and the patient's return to normal (ability to perform on mental function tests) occurs at about four hours after administration of midazolam. The oral dose of midazolam is 10-15 mg.23 According to the product manufacturer, the recommended adult dose of midazolam as an IM injection is 0.07-0.08 mg/kg.26 Midazolam is rapidly absorbed from intramuscular sites and does not produce significant pain or local irritation. The maximum plasma concentration is reached in about 30 minutes.

The onset of sedative effects is 15-20 minutes after injection and the duration of sedative action is 60 to 90 minutes.24 When compared to hydroxyzine 1.5 mg/kg as an intramuscular premedicant,25 midazolam 0.08 mg/kg proved superior for up to one hour after injection in terms of sedative, amnesic and anxiolytic properties. Furthermore it did not cause pain on injection or local irritation.25

According to the product manufacturer midazolam can be titrated intravenously for conscious sedation in a dose range of 0.035-0.15 mg/kg.26 A
5 mg IV dose produced lack of recall and marked sedation within one to two minutes for Conner et al. and this effect lasted approximately 30 minutes. The most frequently reported complaint in this study was dizziness or light-headedness. Pain on injection was absent in 92% of the patients and there was no evidence of thrombophlebitis 24 hours after the injection.

Other Uses. Midazolam has been investigated as an adjunct in a variety of clinical settings including sedation for placement of regional blocks, endoscopic procedures, dental procedures, cystoscopy, cardiac catheterization and angiography. Reports favor midazolam over diazepam for these types of procedures for fairly consistent reasons: (1) shorter onset and duration of action; (2) absence of pain on injection; (3) greater amnesic effects; and (4) good patient acceptance.

Adverse effects. Although the incidence of side effects is relatively low, some of the more commonly reported adverse responses include nausea and vomiting occurring in 0-19% of the patients in the first 24 hours after anesthesia and surgery. The manufacturer reports an incidence of hiccoughs in 5.6% of the patient population, coughing in 1.5%, and nausea and vomiting in 3%. This incidence covers 1,130 patients in 74 studies. The overall incidence of pain on injection and thrombophlebitis is significantly less with midazolam when compared to diazepam but similar to the incidence with thiopental.

Drug interactions in anesthesia

As with any agent used in the practice of anesthesia, midazolam is subject to some noteworthy drug interactions of concern to the anesthetist. Premedication combinations of midazolam and scopolamine enhance and prolong the effects of midazolam when compared to midazolam alone. Opiate premedicants decrease the induction dose of midazolam and shorten time to induction. Recovery may be prolonged with concurrent use of midazolam and central nervous system depressants such as the potent analgesics.

The MAC of halothane is reduced by midazolam in a dose-related fashion. Large doses of midazolam (0.6 mg/kg) have been shown to decrease the MAC of halothane by 30% in healthy humans. However small doses have negligible effects.

Enzyme inhibitors such as the commonly used cimetidine have an effect on the first pass metabolism and elimination of midazolam in the liver. The clinical significance of this effect remains to be examined.

Another drug interaction of special interest is the development of a specific benzodiazepine antagonist, RO15-1788. This agent, which is still under investigation, effectively reverses the behavioral and electroencephalographic effects of midazolam. Also, the acetylcholinesterase inhibitor phystostigmine in combination with glycopyrrolate has been reported to reverse the effects of midazolam.

Lastly, there has been a report of aminophylline reversing the effects of midazolam. This is not surprising because aminophylline has been shown to reverse the effects of the benzodiazepine, diazepam.

Summary

Midazolam is a unique benzodiazepine with important advantages over the currently available benzodiazepines. Its water solubility, quick onset and rapid metabolic clearance set it aside from the traditional agents in this drug category. However, it also possesses the valuable hypnotic, amnesic and anxiolytic effects of the benzodiazepines. Midazolam has a variety of perioperative uses including: effective sleep-inducing properties, helpful the evening prior to surgery; valuable premedication effects desirable in the surgical patient; usefulness as an induction agent and adjunct to maintenance of anesthesia; and sedative effects that are beneficial during diagnostic and therapeutic procedures. Midazolam should serve as a versatile adjunct agent providing it proves worthy in the clinical anesthesia setting.

REFERENCES


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