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Midazolam: Pharmacology and Uses

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MIDAZOLAM, an imidazobenzodiazepine derivative, is utilized as a premedicant, sedative, and an anesthetic induction agent. The unique chemical structure of midazolam confers a number of physicochemical properties that distinguish it from other benzodiazepines in terms of its pharmacologic and pharmacokinetic characteristics.[1] The drug was synthesized in 1976 by Fryer and Walser.[2]

Chemical Properties

Midazolam (molecular wt = 362) has a fused imidazole ring that is different from classic benzodiazepines (fig. 1). The imidazole ring accounts for the basicity, stability of an aqueous solution, and rapid metabolism.[3] The pK_a of midazolam is 6.15, which permits preparation of salts that are water soluble.[3] The parenteral preparation of midazolam used in clinical practice is buffered to an acidic *p*H (3.5).[1,3] Clinical studies of midazolam have been performed with the drug prepared either as hydrochloride or maleate salt. The clinical implications of these different formulations are not established, but they are not likely to be important. In acidic aqueous media, midazolam is water soluble, thereby allowing the parenteral formulation to exclude lipoidal substituents such as propylene glycol. As such, midazolam causes minimal, if any, local irritation after intravenous or intramuscular injection. At physiologic *p*H, on the other hand, midazolam becomes highly lipophilic, and is one of the most lipid soluble of the benzodiazepines.[4,5] It is compatible with D_5W, normal saline, and lactated Ringer's solution and can be mixed in a syringe with acidic salts of other drugs (*e.g.*, morphine, scopolamine, and atropine). The high lipophilicity has a number of clinical consequences, including rapid absorption of midazolam from the gastrointestinal tract and rapid entry of midazolam into brain tissue after intravenous administration. Some studies suggest that opening of the benzodiazepine ring may occur when midazolam is in acidic solution. However, this physiochemical change probably is of minor importance, since the ring opening occurs only to a minor extent and is reversible.[3]

Similar to most benzodiazepines, midazolam is bound extensively to plasma proteins. In plasma from healthy human subjects, the degree of binding averages 96–97% and is independent of the dose and plasma concentrations of midazolam.[6,7] Owing to this extensive binding, the *in vivo* pharmacokinetic properties of midazolam

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must take into account and correct for the extent of plasma binding.[8]

Pharmacodynamics

Effects and Mechanism of Action

Midazolam has the anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and antegrade amnestic effects characteristic of benzodiazepines. The potency of midazolam relative to other benzodiazepines depends on the species and particular effect examined; in humans midazolam is approximately one and one-half to two times as potent as diazepam. The molecular mechanisms underlying the diverse actions remain unclear,[9,10] although some of the mechanisms and sites of action of benzodiazepine's effects are known[10-15] (fig. 2).

Midazolam has an anxiolytic effect. In rats and squirrel monkeys, midazolam diminishes punished behavior (a laboratory measure of anxiety) less than diazepam, apparently because of a more pronounced hypnotic component.[16] The mammillary body may be the site of antianxiety activity, since bilateral injection of midazolam into the posterior hypothalmus mammillary bodies increases the punished response without a change in the unpunished responses.[17] Presumably midazolam exerts its anxiolytic effect like other benzodiazepines by increasing the glycine inhibitory neurotransmitter. The affinity of the benzodiazepines for glycine receptors in the brain stem correlates with their antianxiety potency.[12]

The hypnotic effect of midazolam probably is related to GABA accumulation and occupation of the benzodiazepine receptor. Specific benzodiazepine receptors were discovered in 1977[18,19] and are found in greatest density in the rat cerebral cortex[20] and, in descending order, the hypothalmus, cerebellum, midbrain, hippocampus, striatum, medulla oblongata-pons, and spinal cord.[21] The benzodiazepine binding sites in the human brain correspond to the rat brain in affinity, stereospecificity, and regional distribution.[21] These binding sites occur mainly in the central nervous system (CNS), possibly accounting for the relative lack of non-CNS effects of the benzodiazepines.[15] Reversible binding occurs at these specific membrane binding sites. Midazolam has a relatively high affinity for the benzodiazepine receptor, roughly two times that of diazepam.[18] The most widely accepted hypothesis for the hypnotic effect of benzodiazepines is that there are separate benzodiazepine and GABA receptors coupled to a common ionophore (chloride) channel.[9] Occupation of both receptors produces membrane hyperpolarization and neuronal inhibition. Midazolam interferes with reuptake of GABA, thereby causing accumulation of GABA.[22] This is consistent with the benzodiazepine–GABA interaction hypothesis, as well as the general hypothesis that anesthesia involves excess GABA at neuronal synapses.[23]

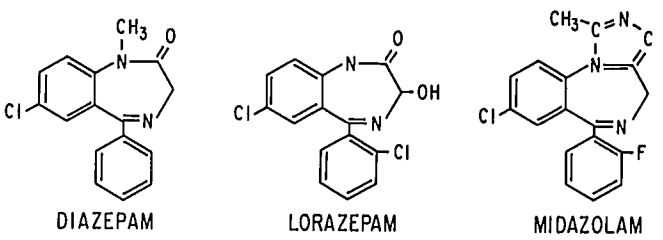


Fig. 1. Structural formulas of midazolam and two commonly used benzodiazepines, diazepam and lorazepam. Note the fused imidazole ring that distinguishes midazolam from other benzodiazepines.

Midazolam anticonvulsant effects are demonstrated in mice by electroshock and antipentetrazole (pentylenetetrazole) tests.[16] A possible mechanism of midazolam's anticonvulsant activity is the enhanced action of GABA on motor circuits in the brain.[12] Midazolam injected (im) in mice reduces the incidence of convulsions and death from an overdose of local anesthetic and is a more effective anticonvulsant than either diazepam or lorazepam.[24] There have been no studies of midazolam's anticonvulsant action in humans, but animal data suggest great potential for this use.

Midazolam impairs motor performance in experimental animals[16] and probably exhibits a muscle relaxant effect similar to the other benzodiazepines. This effect is mediated through glycine receptors in the spinal cord.[12] However, in anesthetized humans, midazolam

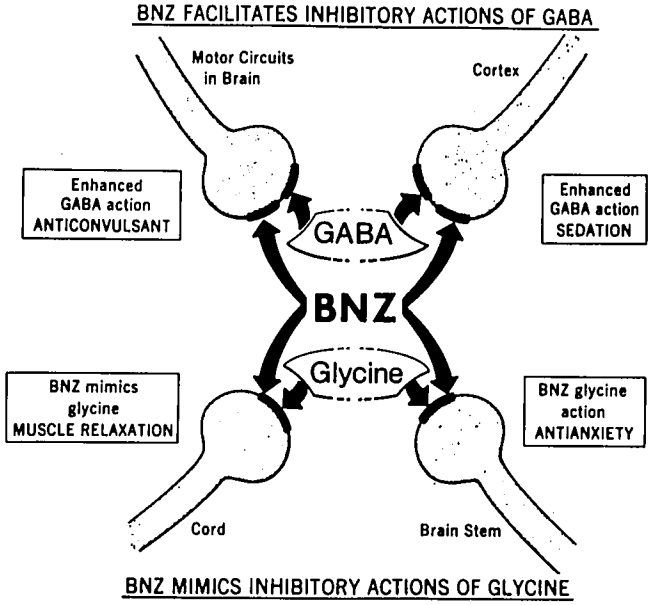


Fig. 2. Mechanisms and sites of action of benzodiazepines. Reprinted from Richter JJ: Current theories about the mechanisms of benzodiazepines and neuroleptic drugs. ANESTHESIOLOGY 54:66–72, 1981, with permission of the publisher.

does not change the dose of succinylcholine or pancuronium necessary to achieve and maintain muscle relaxation.[25,26]

Midazolam, like other benzodiazepines, produces antegrade amnesia. The incidence and duration appear to be related directly to the dose of midazolam.[27] Its site and mechanism of the amnestic action are not known. The degree of amnesia often, but not always, parallels the degree of drowsiness produced by midazolam,[28] and the drowsiness seems to outlast amnesia.[29] The amnestic effect of an intravenous dose of midazolam, 5 mg, ranges from 20[28] to 32 min.[30] Intramuscular administration may prolong the amnestic effect.[31] The amnestic effect of midazolam may be more intense than diazepam but shorter lasting than lorazepam.[32] Prolonged amnesia could be a problem in outpatients by interfering with their ability to recall oral instructions; however, in this setting, amnesia with midazolam lasts no longer than with thiopental.[33]

Midazolam given by intrathecal or epidural injection can produce antinociceptive effects.[34] This could be GABA-mediated because GABA has been shown to have analgesic properties. Perhaps this is the mechanism by which midazolam decreases the MAC of halothane in humans.[35] However, midazolam should not be considered a potent analgesic compound like opioids.

Reversal with Benzodiazepine Antagonist

The behavioral and CNS electrophysiologic effects of midazolam are antagonized by the benzodiazepine antagonist, RO 15-1788.[36,37,¶] In humans, RO 15-1788, 10 mg iv, promptly (30–50 s) awakens subjects receiving a continuous infusion of midazolam. Full orientation[38] and electroencephalogram (EEG) return almost to the predrug state within 5 min[39] after administering the antagonist. The specific benzodiazepine antagonists[40] effectively will reverse CNS depression from midazolam. The clinical effects of midazolam also have been pharmacologically reversed with physostigmine, 2 mg, and glycopyrrolate, 0.2 mg.[41] This is a nonspecific (nonbenzodiazepine receptor) antagonism, since physostigmine can reverse many other CNS depressants via its cholinergic mechanism (*i.e.*, inhibition of acetylcholinesterase).

Cerebral Effects—Hypoxic Brain Protection

Midazolam reduces, in a dose-related manner, cerebral metabolic rate for oxygen (CMR_{O_2}) and cerebral blood flow (CBF). This parallels the behavioral and electroencephalographic effect in dogs[42] and humans.[43]** Midazolam maintains a relatively normal ratio of CBF to $CMRO_2$.†† In normal humans, midazolam, 0.15 mg/kg, induces sleep and reduces CBF 34%, despite a slight rise in Pa_{CO_2} from 34 to 39 mmHg.[43] The presumed explanation for the reduction in CBF is the reduction in CMR_{O_2}. Midazolam also affects the EEG: the rapid appearance of beta activity at 22 Hz associated with the disappearance of the alpha rhythm within 15–30 s is followed 30–60 s later by a second beta rhythm at 15 Hz.[44] The EEG changes are similar to diazepam's EEG effects and not typical of light sleep. Although all patients are conscious and oriented to place and time 19 min after midazolam (10 mg iv), rhythmic beta activity persists for 60 min.[44]

The reductions in CMR_{O_2} and CBF suggest that midazolam can protect against cerebral hypoxia and be useful for patients who have impaired intracranial compliance or increased intracranial pressure (ICP). Midazolam caused a dose-related protective effect against cerebral hypoxia, demonstrated by extending mouse survival time when mice were placed in 5% oxygen.[42] The protection afforded by midazolam is superior to diazepam but less than pentobarbital.[42]

Patients who have intracranial mass lesions and hydrocephalous[45] and those who demonstrate abnormal (decreased) intracranial compliance[46] show little change in ICP when given midazolam in doses of 0.15 mg to 0.27 mg/kg. There is a slight decrease in cerebral perfusion pressure (CPP = MAP − ICP) after midazolam, since systemic pressure tends to decrease more than ICP. Midazolam, 0.15 mg/kg, does not protect against increases in ICP after ketamine or intubation.[45,46] These data suggest that midazolam is an acceptable alternative to barbiturates for induction of anesthesia in patients who have intracranial pathology, and it is possible that midazolam may be of value in protecting the brain against ischemic insult.

Effects on Respiratory System

Midazolam produces some respiratory depression.[11,47–51] In healthy humans, midazolam, 0.15 mg/kg, significantly reduces the ventilatory response to CO_2 and significantly reduces the mouth occlusion–pressure response to CO_2.[11] The slope of the ventilatory response curves to CO_2 is flatter than normal. Peak decrease in minute ventilation after midazolam, 0.15 mg/kg, is almost identical to that produced in normal patients given diazepam, 0.3 mg/kg.[11] The time course and degree of this depression

¶ Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo(1,5-a)(1,4)benzodiazepine-3-carboxylate.

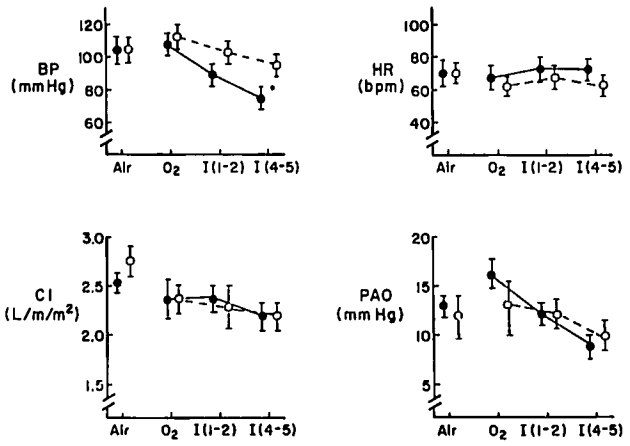
** Larsen R, Hilfiker O, Schenk HD, Radke J, Sonntag H: The effects of midazolam on cerebral blood flow and oxygen consumption. 7th World congress of Anaesthesiologists. Abstracts. Edited by Rugheimer E, Wawersik J, Zindler M. Amsterdam, Excerpta Medica, 1980, p. 302.

†† Michenfelder JD: Brain hypoxia: Current status of experimental and clinical therapy. Seminars in Anesthesia 2:81–90, 1983.

differs between normal humans and patients who have chronic obstructive pulmonary disease (COPD).[51] The peak decrease in the slope of the CO_2 response curve occurs 3.5 min after midazolam, 0.2 mg/kg, when given to healthy volunteers and in 2 min to COPD patients. The return of the CO_2 response curve toward predrug levels is two times faster in normal patients than in those who have COPD. Midazolam respiratory depression in both normal and COPD patients has a slower onset and is more prolonged than with thiopental (3.5 mg/kg).[50]

Respiratory depression following midazolam seems to be a CNS effect, since both the ventilatory response to CO_2[11,48,50] and the mouth occlusion pressure to CO_2[11] are depressed and there is little effect on respiratory mechanics.[52] In laboratory studies using both exposed and desheathed phrenic nerves, midazolam promptly reduced efferent activity.[53,54] The respiratory depressant effects of midazolam are not reversed by naloxone.[47] Interestingly, repeated equal doses of midazolam, 0.1 mg/kg, seemed to produce less depression of the efferent phrenic nerve activity and for a shorter duration, suggesting "tolerance" to the respiratory depressant effects of midazolam.[54] Whether this form of acute tolerance occurs in humans is not known. There is evidence from volunteers that the low sedative doses of midazolam, 0.075 mg/kg iv, do not affect the ventilatory response to CO_2,[55] suggesting perhaps that, in lower doses (*e.g.*, doses used for premedication or sedation) clinically important respiratory depression does not occur. Further investigations are necessary to examine the interactions between midazolam and narcotics, as well as other drugs used in the perioperative period, since it is probable that midazolam will produce additive respiratory depression when used in conjunction with other CNS depressants.

A final respiratory effect of particular concern is apnea. Pooled data from 74 investigations encompassing 1,130 patients given varying doses of midazolam reported apnea in 221 (20%), a significantly ($P < 0.05$) lower incidence of apnea than the 157 out of 580 (27%) control patients given equivalent induction doses of thiopental.‡‡ The incidence of midazolam-induced apnea reported in published papers ranges from 18 to 78%.§§[56–58] Apnea probably is dose related and also a function of the speed of injection: the higher the dose and the more rapid the administration, the higher is the probability that apnea will occur after midazolam, ≥0.15 mg/kg. The duration of the apnea was not affected greatly by dose (17 s 0.05 mg/kg, 19 s 0.1 mg/kg, and 22 s 0.2 mg/kg, respectively). Apnea is more likely to occur after midazolam is given to patients premedicated with opioids.[59]



Where, • = Midazolam, ○ = Diazepam, *P < .05 Midazolam vs Diazepam

FIG. 3. Hemodynamic variables in patients with ischemic heart disease anesthetized with midazolam (0.2 mg/kg iv) and diazepam (0.5 mg/kg iv). HR = heart rate; BP = mean blood pressure; CI = cardiac index; PAO = pulmonary artery occluded pressure. Determinations were made breathing room air (air), breathing 100% oxygen (O_2), 1 to 2 min after intubation (I 1–2), and 4–5 min after induction (I 4–5). Reprinted from Reves *et al.*: Midazolam, New Pharmacologic Vistas in Anesthesia. Edited by Brown BR Jr, Blitt CD, Giesecke AH. Philadelphia, FA Davis, 1983, pp 147–162, with permission of the publisher.

CARDIOVASCULAR EFFECTS

The hemodynamic effects of midazolam have been studied thoroughly.[58,60–71] In normal humans, midazolam, 0.15 mg/kg iv over 15 s, produces statistically significant reductions in systolic (5%) and diastolic (10%) blood pressure and increases in heart rate (18%).[58] These hemodynamic changes are similar to those seen in premedicated patients who have coronary artery disease given doses ranging from 0.2 to 0.3 mg/kg.[60,62,64,65,67] The cardiac index and left- and right-heart filling pressures usually are maintained after midazolam,[61,62,64,65] but the systemic vascular resistance may decrease 15–33%.[62,64,65] Hemodynamic changes after midazolam, 0.3 mg/kg iv, are similar to those seen with hypnotic doses of thiopental, 3–4 mg/kg.[60,61,64] Compared with diazepam, midazolam produces a greater decrease in blood pressure and slightly greater decrease in systemic vascular resistance[65] (fig. 3). Hemodynamic changes after midazolam induction are similar to those following flunitrazepam.[69]

The severity of a patients' cardiac disease does not appear to significantly influence the hemodynamic response to induction with midazolam. In patients who have elevated pulmonary artery occluded (PAO) pressure

‡‡ Data on File, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

§§ Fragen RJ, Gahl F, Caldwell N: RO 21-3981 for induction of general anesthesia. Abstracts of Scientific Papers, 1977 ASA Annual Meeting, p. 423.

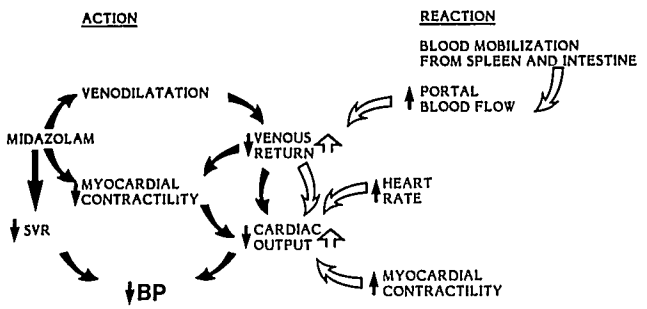


FIG. 4. Schematic representation of the acute hemodynamic effects of midazolam (*solid arrows*) and the homeostatic reflex response (*open arrows*). Note that midazolam decreases blood pressure by several mechanisms: a decrease in SVR, a decrease in venous return, a decrease in contractility, and a decrease in cardiac output. An almost immediate reaction is mobilization of splanchnic blood to the central circulation and baroreceptor-mediated increase in heart rate and contractility, which all return cardiac output to normal. Redrawn from Gelman S, Reves JG, Harris D, Circulatory response to midazolam anesthesia: Emphasis on canine splanchnic circulation. Anesth Analg 62:135–139, 1983.

(>18 mmHg) and reduced cardiac index (CI) (<2.0), induction with midazolam, 0.2 mg/kg, is associated with a reduction in PAO and a return of the CI to normal.[63] Patients with valvular heart disease (n = 8) who had a PAO > 19 mmHg and an ejection fraction < 0.5 maintained stable hemodynamics after receiving midazolam, 0.2 mg/kg.[67] When midazolam was given to ASA class III[68,70] and IV[68] patients, the MAP was reduced 6 to 16%, similar to changes in healthy patients and patients who have cardiac disease. This is comparable to the effect of thiopental, 3 mg/kg[68] but slightly greater than that of diazepam, 0.25 mg/kg.[70]

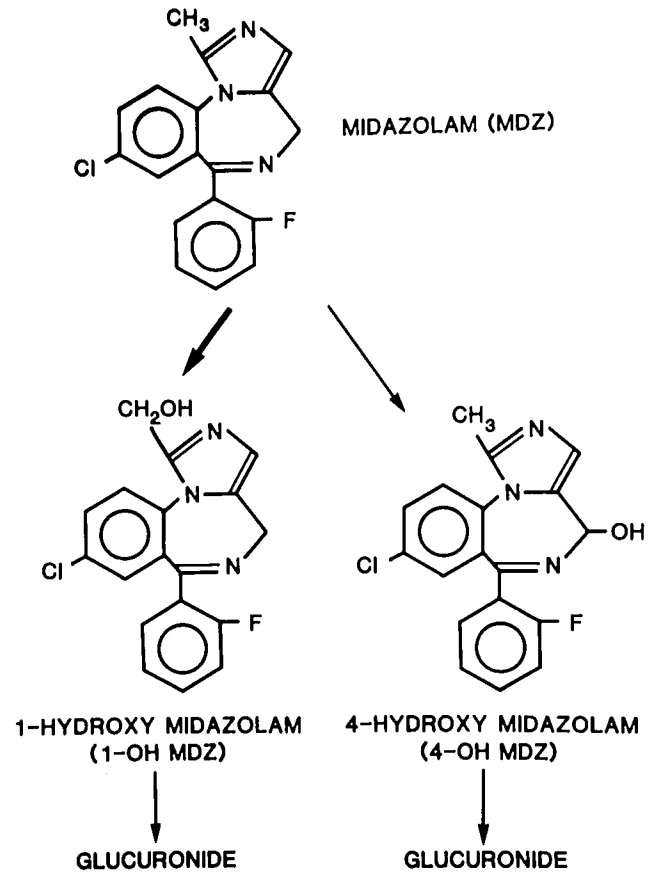


FIG. 5. Metabolic pathway of midazolam in humans.

The cardiovascular pharmacology of Midazolam involves direct and indirect (reflex) action (fig. 4). A decrease in systemic vascular resistance (SVR), venodilation,[66] and a transient change in portal blood flow[72] combine to reduce cardiac filling. Midazolam also decreases myocardial contractility by direct action, as demonstrated by a decrease as in the canine heart LV dP/dt_{max}[73] and isolated rat heart LV dP/dt_{max}.[74] In humans anesthetized with halothane 0.5% and fentanyl, 10 μg/kg, midazolam, 0.3 mg/kg, reduced the LV dP/dt_{max}.[75] A reduction in blood pressure presumably activates the baroreflexes, simultaneously increasing heart rate and contractility with mobilization of splanchnic and other blood volumes into the central circulation. Although there is some evidence that midazolam attenuated the catecholamine response to hypotensive stress,[76,77] it is clear that preservation of hemodynamic function occurred with midazolam.[76] This involved an intact sympathetic reflex, as demonstrated by release of endogenous catecholamines.[76] In unanesthetized animals, a 40-fold increase in the dose of midazolam (from the subanesthetic dosage of 0.25 mg/kg up to the suprahypnotic dose of 10 mg/kg) caused few dose-related reductions in hemodynamic variables,[73,78] indicating a relatively wide safety margin.

In humans, the hemodynamic response to induction of anesthesia with midazolam is a slight decrease in blood pressure; when intubation follows induction, however, significant increases in heart rate and blood pressure occur.[60,65] These are smaller increases than with thiopental[60] and may be attenuated but not completely blocked with 50% N_2O in oxygen.[65] Fentanyl, 5–7.5 μg/kg, given prior to midazolam induction, blocks the tachycardia and hypertension secondary to intubation.[67] Thus, additional analgesics or anesthetics are required to attenuate the sympathetically mediated hemodynamic responses to intubation in midazolam-induced patients.

Metabolism and Pharmacokinetics

BIOTRANSFORMATION

Metabolism of midazolam in humans involves hydroxylation by heptic microsomal oxidative mechanisms (fig. 5). The fused imidazole ring is oxidized very rapidly by the liver, much more rapidly than the methylene group

of the diazepine ring of other benzodiazepines.[3] The principal metabolite is 1-hydroxymidazolam (1-hydroxymethylmidazolam).[3,16,79-81] Smaller amounts of 4-hydroxymidazolam are formed in parallel, and even smaller amounts of 1,4-dihydroxymidazolam can be detected. These metabolites are excreted in the urine in the form of glucuronide conjugates. Very little intact drug is excreted unchanged in the urine. The 1-hydroxy and, to a lesser extent, the 4-hydroxy, metabolites of midazolam are present in human blood in the unconjugated form after administration of the parent compound. The 1- and 4-hydroxy metabolites of midazolam have pharmacologic activity, although less than that of the parent compound.[16,82] Their contribution to the overall clinical effect of midazolam is not established nor is their relative potency or precise duration of effect.

Pharmacokinetic Properties

The high lipophilicity of midazolam at physiologic *p*H causes it to have a very rapid onset of activity after intravenous administration. In experimental models, the drug rapidly enters the cerebrospinal fluid (CSF), and equilibration between plasma and CSF generally occurs within a few minutes of intravenous amdinistration.[5] Midazolam's entry into brain tissue and the onset of clinical effects are correspondingly rapid.[5] The high lipophilicity of midazolam, coupled with its very high metabolic clearance and rapid rate of elimination, cause it to have a short duration of activity. The termination of action after single doses is caused both by distribution into peripheral tissues and by metabolic biotransformation.

After intravenous administration of midazolam to healthy young humans of normal body habitus, the disappearance of midazolam from the plasma proceeds in at least two distinct phases (fig. 6). The initial phase of rapid disappearance is due principally to distribution of the drug, while the final and slower phase of disappearance is attributable mainly to biotransformation. In healthy individuals, midazolam's volume of distribution generally averages between 1 and 2.5 l/kg.[7,82-88] It should be noted that midazolam is bound extensively to plasma protein[6] and that the volume of distribution estimated on the basis of the total drug in plasma (*i.e.*, bound and free) underestimates the actual distribution of the unbound form that is pharmacologically active. After the distribution equilibrium is achieved, elimination of midazolam proceeds rapidly, with a half-life ranging from 1 to 4 h in healthy young humans of normal body habitus.[7,83-88] There is potential for drug accumulation with repeated doses. The total clearance of midazolam is approximately 50% of the hepatic blood flow. Thus, midazolam is a widely distributed and very rapidly

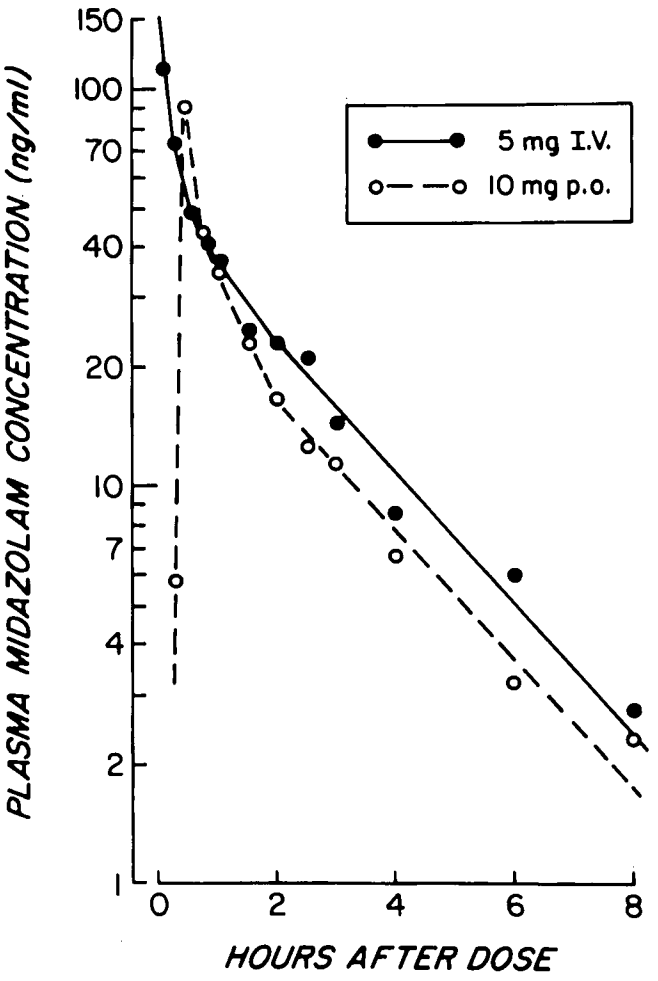


FIG. 6. Plasma midazolam concentrations after a single 5-mg intravenous dose and a single 10-mg oral dose administered to a healthy young volunteer of normal body habitus on different occasions. Data taken from Greenblatt *et al.*: Importance of protein binding for the interpretation of serum or plasma drug concentrations. J Clin Pharmacol 22:259-263, 1982.

cleared benzodiazepine.[89,90] The termination of clinical effect after a single intravenous dose is also rapid, because of the combination of extensive distribution and rapid clearance. The precise degree to which clearance and redistribution contribute to cessation of midazolam effect has not been investigated as Burch and Stanski did with thiopental.[91] There is a reasonably good association between the plasma midazolam level and psychologic performance (r = 0.68-0.92) and subjective sedation (r = 0.62-0.95).[92]

The major difference in pharmacokinetics between midazolam and diazepam can be seen in table 1. The distribution half-life of midazolam is at least one-half that of diazepam and the elimination half-life is about tenfold less. The volumes of distribution are relatively similar, probably reflecting their lipid solubility. The total body clearance of midazolam is much higher than

TABLE 1. Comparison of Pharmacokinetic Variables

	Diazepam	Midazolam
$t_{1/2}a$ (min)	30–60	6–15
$t_{1/2}b$ (hrs)	24–57	1.7–4
Vd (l/kg)	0.7–1.7	1.1–1.7
Cl (ml/min/kg)	0.24–0.53	6.4–11.1

Data from Reves JG: Benzodiazepines, Pharmacokinetics of Anesthesia. Edited by Prys-Roberts C, Hug CC Jr. Oxford, Blackwell Scientific Publications, 1984, pp 157–186.

diazepam. In short, the pharmacokinetics of midazolam indicate a short-lived compound *versus* a relatively long-lived one, diazepam. Since pharmacodynamic effects are related to drug levels, midazolam CNS effects might be expected to be of shorter duration than after equieffective doses of diazepam.

After oral administration, midazolam is absorbed very rapidly from the gastrointestinal tract (fig. 6).[7,83–85,87] Peak plasma concentrations generally are achieved within 1 h of ingestion, and the onset of clinical effects after oral administration is correspondingly rapid. Owing to the rapid hepatic clearance of midazolam, the absolute systemic availability after oral administration is significantly less than 100%. On the average, only 40–50% of an orally administered dose reaches the systemic circulation in its nonmetabolized form. This is because of extensive first-pass hepatic extraction. Thus, the oral dose of midazolam must be approximately twice as high as the intravenous dose to achieve comparable clinical effects. The elimination half-life of oral midazolam, on the other hand, is similar or identical to that observed after intravenous administration, indicating that the rate of elimination is independent of the route of administration.

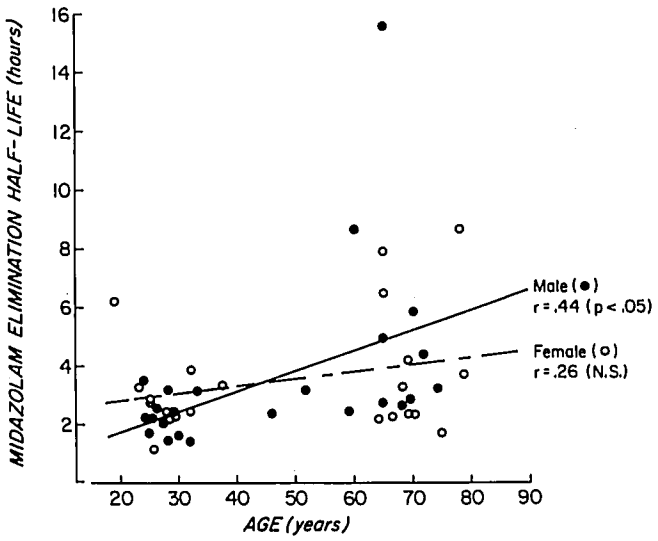


FIG. 7. Relation of age to midazolam elimination half-life in men and women.

Schemes for intravenous infusion have been devised whereby a constant plasma concentration of midazolam can be achieved and maintained.[93] Such schemes may prove valuable, should midazolam ultimately be used as an anesthetic drug given by continuous infusion. It is also known that midazolam, when given in very large doses to animals, crosses the placenta, and that fetal and maternal distribution and elimination kinetics are similar.[94] If given to pregnant women, midazolam would be expected to appear in the fetus,[88] but effects on the human fetus are not known.

Factors Influencing Pharmacokinetics. Previous studies of the pharmacokinetics of benzodiazepines in the elderly suggested an impairment in total metabolic clearance of those benzodiazepines biotransformed by hepatic microsomal oxidation.[95] In some studies, this limited metabolism has been more evident in elderly men than in elderly women.[95] Similar results are described for midazolam, consistent with the fact that its biotransformation pathway is principally by microsomal oxidation. In one study, involving a series of elderly as opposed to young male volunteers, midazolam's elimination half-life was prolonged more than twofold and total metabolic clearance was reduced correspondingly.[7] In women, there also was a prolongation of the half-life and a reduction of the total clearance associated with age, but the age-related changes did not reach statistical significance (fig. 7).[7] The volume of distribution was increased slightly in the elderly,[7,96] and the volume of distribution was larger in women than in men, regardless of age.[7] Since the volume of distribution is a major determinant of the intensity and duration of midazolam's activity after a single intravenous dose, these studies suggest that a reduction in the dose of midazolam for elderly patients is not required, based on pharmacokinetics alone. Since continuous infusion is based on patient's clearance, infusion rates in elderly men should be reduced by approximately 50% to compensate for their reduced clearance.

The pharmacokinetic profile of midazolam is altered significantly when the drug is administered to morbidly obese individuals.[7] The volume of distribution increases greatly in obese patients because of the greatly enhanced distribution of midazolam into peripheral adipose tissues. This in turn causes a highly significant prolongation of the elimination half-life but no change in the total metabolic clearance. For obese patients, each single intravenous dose of midazolam should be increased at least in proportion to total body weight. The rate of continuous infusion, however, should be adjusted to the ideal rather than the total weight.

Because renal clearance of intact midazolam contrib-

utes very little to its total elimination, one would expect minimal alteration of midazolam's clearance in patients who have renal insufficiency. This was confirmed by a study of midazolam kinetics comparing 14 patients who had renal failure with 14 age, sex, and weight-matched controls.[97] The free fraction of midazolam in the plasma was increased significantly in renal-failure patients, consistent with the reports of reduced plasma binding of other benzodiazepines in such patients.[98–101] After correcting individual values for the free fractions, there was no significant difference between control and renal-failure patients in midazolam's volume of distribution, clearance, or elimination half-life.

Uses

Induction of Anesthesia

Midazolam may be used intravenously for the induction of anesthesia (table 2). Induction is accomplished when there is unresponsiveness to command and loss of the eyelash reflex. As an induction drug, midazolam produces sleep and amnesia but it does not have a great analgesic effect. Midazolam is not as rapid acting as thiopental; at approximately equipotent (loss of unconsciousness) doses, thiopental abolishes the eyelash reflex 50–100% faster than midazolam.[56,102–106] Also, in comparison to thiopental, the response to a given dose of midazolam is more variable. However, at higher doses of each drug, this variability greatly is reduced.[102] The differences in induction times as well as the interpatient variability in response make the induction of anesthesia less predictable, but it is well accepted by patients.

Dose and Rate of Administration. There are a number of factors that affect the induction of anesthesia with midazolam. The success of and rapidity of the induction are related directly to dose.[107] The induction dose of midazolam ranges from 0.1 mg to 0.4 mg/kg.[56,58,59,108,109] Doses of 0.2 mg/kg have been given safely in less than 30 s, even in high-risk patients.[62,110] In a small study involving healthy females, the 95% effective dose (ED_{95}) for induction in unpremedicated patients was 0.2 mg/kg iv when given rapidly over 5–15 s.[108] The ED_{95} is not universally applicable, and one factor that might explain the marked variability in dose-finding studies is that many studies were "dose-seeking" in which low, initial doses (0.1–0.15 mg/kg) were followed by titration of 20–25% of the initial dose at subsequent time intervals. This method of administration takes longer and produces higher total doses, since slow administration permits rapid distribution of the drug and does not present a high drug concentration to the CNS. Whether acute tolerance also develops is not known. The importance of the speed of injection is apparent when assessing the difference between the following two studies. White, using 0.3 mg/kg, induced anesthesia in 30–60 s[105]; Finucaine[111] gave the same total amount, but in four incremental doses at 2-min intervals and took 4.9 min to induce anesthesia.

TABLE 2. Perioperative Uses of Midazolam

Effect	Dosage	Route
Induction	0.15–0.40 mg/kg	iv
Maintenance	Titration*	iv
Premedication	0.07–0.10 mg/kg	im
	10–15 mg	po
Intravenous sedation	Titration†	iv
	0.05–0.15 mg/kg	

* To desired end points.
† to dysarthria.

Influence of Premedication. The dose of midazolam required to induce anesthesia is higher in unpremedicated healthy patients (up to 0.3 mg/kg) than in premedicated patients.[105,112] Opioids, such as fentanyl[113] and alfentanil,[114] are effective in facilitating induction with midazolam. The large interindividual variation in response to induction with midazolam can be reduced markedly in a dose-related fashion: the more opiate the patient receives, the more rapid and predictable the induction of anesthesia.[25,56,58,103–107,115–116] This premedication may be given either intramuscularly or orally an hour or so prior to induction of anesthesia or as an intravenous dose immediately before anesthesia.[62,65] The use of the benzodiazepines or other sedative–hypnotic premedicants does not produce the same enhanced effect as the narcotics and does not reduce midazolam's induction time or required dose.[67,111]

Effect of Age and ASA Status. Age affects induction with midazolam. Elderly patients (62–76 years of age) require less midazolam than young, healthy patients.[116] This enhancement of the benzodiazepines' action in the elderly cannot be explained pharmacokinetically. Although the half-life is prolonged in the aged, this should not affect the acute, hypnotic effect of a single, intravenous dose. A possible explanation is the possibility of an increase in CNS activity in the elderly.[95]

The relationship between ASA physical status and the dose of midazolam required to induce anesthesia is not known, but some evidence indicates that ASA III and IV patients require less midazolam[68]: reported doses range from 0.15 to 0.2 mg/kg.[62,110,117] There is a combined effect of age over 55 and ASA status > III, since patients in this group require about 20% less midazolam than younger, fit patients.¶¶ There has not been a systematic study of the effect of other disease states on the action of midazolam; however, renal failure

¶¶ Data on File, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

has been studied. Anesthesia is induced more rapidly in chronic renal failure patients; they also may sleep longer than normal patients.[97] Pharmacokinetics partially may explain this, since there is more unbound (active) drug available to the CNS receptors because of the lower binding of midazolam to albumin in renal failure patients: there is almost twice as much unbound midazolam (7%) in renal failure patients than in normals (4%).

Influence of Gender. Male patients seem to be more sensitive to midazolam than female patients.[58] They lose the eyelash reflex sooner than female patients and have greater amnesia, greater subjective drug effect, more frequent apnea, and delayed emergence (opening of the eyes) after the injection than female patients. This apparent reduction of hypnotic effect in female patients may be due either to a decreased sensitivity or possibly an increased initial volume of distribution as compared with male patients.

Emergence. The emergence of young, healthy volunteers who have received midazolam, 10 mg, defined as orientation to time and place, occurs in about 15 min.[44] Careful analysis of the emergence from intravenous midazolam, 0.15 mg/kg, reveals that 75% (15 out of 20) of healthy volunteers open their eyes spontaneously 17 min after administration of the drug.[59] Sixty per cent have fair walking ability after 22 min, and 60% can read relatively well after 1 h, but 20% read poorly.

When emergence is evaluated after general anesthesia and surgery, considerable variability exists. Compared with patients who received thiopental for induction, awakening ranges from one and one-half to two and one-half times as long with midazolam.[25,57,106,112] The addition of potent opiates tends to prolong the recovery from midazolam.[50] However, fentanyl, 1.5 μg/kg, did not prolong recovery when given immediately before induction.***

Maintenance of Anesthesia

Midazolam is a useful hypnotic–amnestic during maintenance of general anesthesia. In double-blind studies comparing midazolam and thiopental induction and maintenance, midazolam proved superior to thiopental because there were fewer adjuvant anesthetics required to maintain an acceptable depth of anesthesia.[25,33] Midazolam also confers more amnesia and evokes better patient and physician acceptance and fewer emergence complications.[25,33] Midazolam cannot be used alone, however, to maintain adequate anesthesia[58,59,114,115]; fentanyl, 1.5–2.0 μg/kg and nitrous oxide 66% are effective supplements. Midazolam also may be used with inhalation drugs; indeed, the MAC of halothane is reduced in a dose-related fashion by midazolam.[35] Small doses have neglible effect, but 0.6 mg/kg of midazolam reduces the MAC of halothane 30% in healthy humans. After use for maintenance of anesthesia, recovery is longer from midazolam than from thiopental.[25] The return of psychomotor skills and performance tests to baseline levels is not statistically different when patients receive thiopental or midazolam.*** Patients can be discharged in 2–3 h in the company of a responsible adult after receiving midazolam.[113]

*** Data on File, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Premedication

Midazolam, like diazepam and the other benzodiazepines, is well-suited for premedication, since it has both anxiolytic and hypnotic properties (table 2). Studies of its hypnotic effect show that the onset of sleep is relatively rapid and the duration of the hypnotic effects and sleep stages are highly variable and dose related.[117] Performance on tests of mental function (the ability to concentrate) returns to normal 4 h after the administration of midazolam.[117]

When midazolam, 5 mg, was given as intravenous premedication, the hypnotic and anxiolytic effects appeared within 1–2 min and a memory picture shown 4 min after injection was not recalled by 78% of the patients. These effects persisted for 30 min.[30] The only prominent side effect from this dose was dizziness or lightheadedness. Midazolam appears to be an excellent drug for the intravenous sedation of anxious patients and for supplementation of inadequate premedication. Midazolam has been administered as an oral premedicant only in Europe[118,119]; this use requires study, but midazolam, 15 mg po, is superior to placebo.[119] A comparison of oral midazolam with other benzodiazepines and premedicants needs to be done: the rapid onset and relatively short-lasting effects of oral midazolam premedication are attractive features.

Pharmacokinetic studies show that there is rapid absorption of midazolam from intramuscular sites.[120,121] Administered intramuscularly, midazolam does not produce significant pain or local irritation. There is a greater hypnotic effect than with a placebo, and a superior anxiolytic effect, as demonstrated by the anxiety visual analog test (AVAT). Curiously enough, however, one study demonstrated little difference between midazolam and the placebo on the AVAT 60 min after injection.[122] Perhaps this was because of a strong placebo effect, the short duration of midazolam's effect, or both. When compared with diazepam, 0.17 mg/kg im, midazolam, 0.13 mg/kg im, produced a faster onset of action and greater sedation and was preferred by patients as a

premedicant.[123] This dose of midazolam produces peak plasma concentrations of 67.8 ± 24.5 ng/ml (mean ± SD).[123] Given intramuscularly 30 min before induction, midazolam, 10 mg, produced a greater decrease in preoperative anxiety than diazepam, 15 mg. The amnesic effect was more profound after midazolam for arrival in the operating room and recovery on the operating table.[124] Midazolam thus has a clear advantage over diazepam when given intramuscularly, probably because of its more predictable absorption.

Midazolam, 0.07–0.08 mg/kg, is superior to hydroxyzine, 1.0–1.5 mg/kg, in terms of its greater hypnotic, anxiolytic, and amnesic effect for up to 1 h after intramuscular injection.[31,125,†††] After the first hour, however, the differences disappear between the drugs' effects. The peak effect occurs 30–45 min after the injection of midazolam. Patients premedicated with midazolam require less thiopental for induction than unpremedicated patients.[125] Scopolamine injected concurrently with midazolam enhances its anxiolytic and amnesic effects.[31] Because of its rapid absorption from intramuscular sites and early onset of effect, midazolam seems especially suited for the first patients on the morning surgery schedule or for patients who will be premedicated less than 1 h before anesthetic induction.

Intravenous Sedation

Midazolam is a useful intravenous adjuvant to local or regional anesthesia for a variety of therapeutic and diagnostic procedures. Titrated intravenously to produce sleep, or more commonly, dysarthria, midazolam produces mild sedation and amnesia in patients for diagnostic and therapeutic procedures. The average dose required is 0.1 mg/kg. Midazolam can be used for the sedation of healthy patients receiving subarachnoid[126] or epidural[127] anesthesia. Sedation occurs without loss of airway reflexes or significant cardiovascular changes.[126] Compared with diazepam, midazolam produces less postoperative drowsiness[126] and more amnesia[126,127] but the time to complete recovery is no shorter.[126,127] Midazolam also is useful for intravenous sedation for endoscopic procedures, including gastroscopy, esophagoscopy, and cystoscopy.[128–134] The onset of sedation is more rapid with midazolam than diazepam, but time of recovery is similar.[134]

Elderly patients have a more consistent response to a given dose,[129] and midazolam produces a more profound amnestic effect in them than diazepam.[134] The amnestic effect is not necessarily correlated with the dose or degree of sedation.[130] Patients questioned postoperatively prefer midazolam to diazepam and have fewer complaints of discomfort during the procedure, probably because of amnesia for the procedure. Patients who receive midazolam tend to be more somnolent at the end of the procedure than those who receive diazepam. Psychomotor tests usually do not return to the control value for 2 h after the administration of either midazolam or diazepam. In addition to amnesia, an advantage of midazolam over diazepam is that there is less pain on injection and less venous irritation. Cardiovascular depression and clinical evidence of respiratory depression are usually absent in patients given midazolam by the titrated intravenous method of administration.

It is difficult to establish the adequacy of local nerve blocks in dental procedures after the intravenous administration of midazolam, 0.1 mg/kg.[135] When half this dose is given before the block and the other half is given afterward, generally acceptable conditions for operation are present. Recovery time of midazolam and diazepam, as measured by the pegboard test, is slightly more than an hour with both drugs.[135]

At a recent symposium on midazolam, it was reported that titrated midazolam and a fixed dose of atropine (0.4 mg) and meperidine (50 mg) was a successful drug combination for sedation during cardiac catheterization and bronchoscopy.[‡‡‡] For these procedures, this combination of drugs caused no untoward cardiovascular or respiratory effects. When compared with a similar drug combination containing diazepam instead of midazolam, patients and physicians rated midazolam as a better sedative–anmesic than diazepam titrated to the same end point. Although not specifically studied in humans, the characteristics of midazolam suggest it would be useful for sedation or hyponsis during cardioversion and electroshock therapy.

Outpatient Use

The relatively rapid onset and brief half-life of midazolam make it a suitable drug for use in short-duration anesthesia.[33,136] Induction with midazolam in a healthy outpatient population is slower than with thiopental.[33,105,113] Adjuvant narcotics or volatile agents are required to maintain adequate anesthesia.[33,102,113] After midazolam, the initial wakening in the recovery room is more prolonged than when thiopental is used,[33] but it is gradual and infrequently associated with nausea, vomiting, or emergence excitment phenomena.[33,113] One hour after surgery, patients are equally alert with either midazolam or thiopental.[33] Discharge time is similar.[113]

††† Miller R, Eisenkraft JB, Thys DM, Toth C, Bohmer FA, Melmed AP: Comparison of i.m. midazolam with hydroxyzine as preanesthetic medications. Anesthesiology Review 9(2):15–19, 1982.

‡‡‡ Data on File, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Novel drug combinations may be used to minimize the slower onset and recovery with midazolam: midazolam and ketamine for induction complement each other.[105] With this regimen there is a rapid induction and quick emergence. Midazolam also effectively attenuates the cardiostimulatory response to ketamine and prevents unpleasant emergence sequelae.[105] Thorton and Hughes[137] found that they could give midazolam, 2.5 mg, intravenously every 30 s to outpatients until ptosis, slurring of speech, or obvious sedation occurred. This technique facilitated a smooth transition to an inhalational anesthetic in an amnesic patient. Thirty-four out of 35 cases responded with their date of birth 10 min after the termination of anesthesia, demonstrating a prompt emergence in the outpatient setting.

For the outpatient, midazolam provides useful amnesia for unpleasant and painful procedures. However, important postoperative instructions may be forgotten and need to be written or given to a responsible, accompanying adult.

Undesirable Effects

Midazolam is remarkably free of side effects. In volunteers who did not receive other anesthetic drugs, nausea and vomiting are absent.[58,138] The incidence of nausea and vomiting after anesthesia and surgery ranges from nil[25,102,105,139] to 15%[105] to 19%[141] in the first 24 h. This higher incidence of nausea and vomiting is similar to the incidence with other drugs. There are, however, no data to support a claim for an antiemetic effect of midazolam. The adverse experiences reported with a frequency greater than 1% in 1,130 patients in 74 studies are hiccoughs, 5.6%, coughing, 1.5%, and nausea and vomiting, 3%.§§§

The reported frequency of local venous complications after the intravenous administration of benzodiazepines varied between 10 and 78%.[141] These complications included pain on injection, thrombosis, and thrombophlebitis. Differences are most likely due to different solvents, but the size of the vein, rate of injection, criteria for defining local reactions, and the time of observation may have influenced the incidence of venous complications. A major advantage of midazolam is its water solubility and low reported incidence of venous irritation and thrombophlebitis. Mikkelson's report of a 9% incidence of thrombophlebitis after saline illustrates that other variables, including the technique of intravenous cannulation, type of catheter used, duration of cannulation, and differences of interpretation among observers affect the incidence. Therefore, the incidence of thrombophlebitis only can be judged in comparative studies. In five separate studies of midazolam, the incidence of thrombophlebitis was nil.[25,44,103,140,142] Two other studies reported an incidence of 8–10%; this is significantly less than with diazepam, but similar to the incidence of thrombophlebitis with thiopental.[106,115]

§§§ Data on File, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Summary

Midazolam is an imidazobenzodiazepine with unique properties when compared with other benzodiazepines. It is water soluble in its acid formulation but is highly lipid soluble *in vivo*. Midazolam also has a relatively rapid onset of action and high metabolic clearance when compared with other benzodiazepines. The drug produces reliable hypnosis, amnesia, and antianxiety effects when administered orally, intramuscularly, or intravenously. There are many uses for midazolam in the perioperative period including premedication, anesthesia induction and maintenance, and sedation for diagnostic and therapeutic procedures. Midazolam is preferable to diazepam in many clinical situations because of its rapid, nonpainful induction and lack of venous irritation. Compared with thiopental, midazolam is not as rapid acting nor predictable in hypnotic effect. It will not replace thiopental as an induction agent.[25] Advantages of midazolam over thiopental are those of the more versatile pharmacologic properties of a benzodiazepine compared with a barbiturate such as amnestic and anxiolytic properties. Midazolam should be a useful addition to the formulary.

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