Midazolam: a review of its use for conscious sedation of children

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Introduction

Much interest has been focused on the use of midazolam (Versed®—Roche Laboratories of Hoffman LaRoche, Nutley, NJ) for conscious sedation in pediatric dentistry. The drug has been used as a preanesthetic sedative in adults and more recently in children. However, studies are lacking concerning its use in pediatric dentistry. The purpose of this paper is to review the pharmacokinetics of midazolam in children and its routes of administration including intravenous, oral, rectal, and nasal routes.

Pharmacology

Pharmacologic structure

Midazolam HCL first was synthesized by Fryer and Walser in 1976.[1] It is a short-acting, water soluble benzodiazepine drug that acts similarly to diazepam (Valium® — Roche Laboratories of Hoffman LaRoche, Nutley, NJ) on GABA- (γ-amino butyric acid) associated benzodiazepine receptors. It has anxiolytic, sedative, hypnotic, anticonvulsant, muscle-relaxant, and anterograde amnesic effects. Its chemical structure is different from classic benzodiazepines such as diazepam, and this is responsible for its unique characteristics of rapid absorption and rapid metabolism.[2] Unlike diazepam, midazolam may be prepared as a water soluble salt that facilitates intravenous (IV) and intramuscular (IM) administration with minimal, if any, local irritation. Once administered, midazolam becomes highly lipophilic. The high lipid solubility enhances rapid absorption and penetration into the CNS. Because of its chemical structure, the drug is oxidized by the liver much more rapidly than other benzodiazepines[2] and, consequently, has a short duration of action.

Kinetics and metabolism

The pharmacokinetics of midazolam in adults has been studied,[3–7] however, the available data in children are limited.[8,9] After midazolam is absorbed from its administration site, it is transported to its action site by the blood plasma. In the plasma, midazolam is bound extensively to plasma proteins and only the unbound drug is pharmacologically active. The drug is metabolized to alpha-hydroxy-midazolam and immediately is conjugated by glucuronic acid to form a pharmacologically inactive end product that is eliminated in the urine. Two other metabolites are excreted in insignificant amounts.[3]

Peak serum concentrations of midazolam are reached at different times in children depending on the administration method.[8] IM and rectal routes peak at 15 and 30 min after administration, respectively, while the oral route serum concentration peaks in less than 1 hr. The metabolic turnover of midazolam in children is more rapid than in adults due to children's more active liver metabolism. The elimination half-life is approximately 45–60 min[8] in a child as compared with 2–6 hr in an adult.[4,5] Midazolam is eliminated significantly faster when compared with diazepam's elimination half-life of 24–57 hr.[6]

An association between the plasma midazolam concentration and the level of clinical sedation has been established in adults[10,11] and in children.[9] Maximum level of sedation in children corresponds to a mean peak midazolam plasma concentration of 229 μg/L. Thereafter, a decline in the sedation level parallels the decrease in plasma midazolam concentration.

Amnesic effects

Initial studies on adults[12] have indicated that midazolam produces a profound anterograde amnesia. For example, more than 75% of patients were amnesic following the passage of an endoscope.[13] Amnesia also was demonstrated in patients treated during dental surgery for more than 4 hr.[14] Although diazepam also has been shown to cause anterograde amnesia, it has significant individual variance. Midazolam produces anterograde amnesia in adults more reliably and for a longer duration than does diazepam or fentanyl.[12]

Oral midazolam, at a dose of 0.5–0.75 mg/kg, produces amnesia in children undergoing surgical procedures.[15] The degree of amnesia is not dependent on the route of administration, as there was no significant difference when the amnesic effect of oral (0.45 mg/kg) was compared with IM midazolam (0.2 mg/kg) in children.[16] Midazolam was found to provide partial or complete amnesia in 90% of children undergoing bone marrow aspirations or lumbar punctures.[17] Significantly fewer children undergoing gastroendoscopy recall pain or discomfort with midazolam compared with diazepam at both 1 and 24 hr following the procedure. More patients receiving midazolam indicated preference for the same sedation for future procedures.[18]

Routes of administration

IV and IM routes

The use of midazolam in adults via the parenteral routes is well documented and is marketed by the manufacturer

exclusively for IV and IM use in adults. When given parenterally,[19] midazolam is preferred to diazepam. Diazepam's absorption after IM injection is slow and erratic and it is often associated with severe pain,[20] whereas midazolam is well-absorbed and is less painful via the IM route. When administered intravenously, diazepam may cause phlebitis and local pain, whereas midazolam does not, due to its increased water solubility. The recommended dose for IV administration of midazolam is between 0.05–0.1 mg/kg, depending on the nature of the procedure (whether premedication, sedation, or general anesthesia induction) and whether other drugs are being used[9, 18, 21] (Table 1).

Table 1. Common pediatric doses

Route	*Dose mg/kg*
Intravenous	0.05 – 0.1
Oral	0.3 – 0.75
Rectal	0.4 – 1.0
Nasal	0.2 – 0.3*

* Repeat dose after 10 min if needed.

Although the IV route is the most effective [8, 9, 18, 19, 21] it is not preferred for children. Parenteral administration is a major cause of anxiety, discomfort, and trauma in children and the trend in pediatrics is to avoid injections whenever possible. Consequently, other routes including the oral, rectal, and nasal routes have been used.

The oral route

Midazolam currently is available in the United States only as an IV solution. It has been used as an oral agent but it has a distinct bad taste that is not easily disguised in apple juice or other clear or carbonated liquids. Various homemade preparations to mask the bad taste have been reported.[8, 15, 22] One useful method uses a 2-quart package of grape flavored Kool-Aid® (Kraft General Foods, Inc., White Plains, NY) with Nutrasweet® (Nutrasweet, Skokie, IL) mixed in only 2 cups of water.[23] The concentrated midazolam (5 ml/mg) at 0.5 mg/kg then is mixed with 5–10 ml of the concentrated grape drink and refrigerated. This formulation takes the bitterness out of the parenteral preparation.

Numerous studies of oral midazolam in children have given conflicting results.[15, 16, 22, 24] A single oral dose of 0.2 mg/kg was found to be effective during laceration repair in the emergency room.[24] However, most studies indicated that a higher oral dose is needed.[8, 15, 16, 25] Only 15–30% of an orally administered dose reaches the systemic circulation in its nonmetabolized form due to an extensive first-pass hepatic effect.[8] Thus, the oral dose should be approximately double or triple the IV dose to achieve similar clinical effects. Oral doses ranging between 0.3–0.75 mg/kg commonly are recommended[8, 15, 25] to be given 20–30 min prior to treatment.

The rectal route

Whereas oral administration requires patient cooperation, the rectal route does not. Children could be told that their temperature is being taken and frequently they will cooperate for the procedure. Most drugs, however, are not as well-absorbed rectally as from the upper intestine.[26] Rectal midazolam has been studied as a preanesthetic medication for children[27, 28] and the optimal sedative dose was determined to be 1.0 mg/kg.[27] Children receiving variable doses of rectal midazolam as high as 5 mg/kg were delayed in discharge from the hospital; however, only one of the 41 patients lost consciousness.

The nasal route

The first study of intranasal administration of midazolam in children was conducted by Wilton in 1988[29] and other studies have been performed since.[30–37] A dose of 0.2 mg/kg–0.3 mg/kg (5 mg/ml, IV solution) in a 1-ml syringe was given. If patients did not show significant sedation in 5 to 10 min, a repeat dose was administered. Higher doses necessitated a larger volume of the drug, resulting in more coughing, sneezing and expulsion of part of the drug. To avoid this problem, administration of the drug was performed in two steps instead of one.[32] Children sedated with intranasal midazolam are passive and moderately drowsy but usually do not fall completely asleep. The average time to peak plasma concentrations and maximal effect is 10 min[31, 32, 36] and recovery time is approximately 30 min, with the degree of the sedative effect similar to that obtained with IM administration.[33] No incidence of significant respiratory depression, emesis, or oversedation has been reported and all vital signs including oxygen saturation remain stable during sedation.

Intranasal midazolam may be used in combination with other drugs in diagnostic and short surgical procedures in children. One technique involved 0.2 mg/kg intranasal midazolam followed by 9.0 mg/kg ketamine administered rectally.[30] Cardiovascular stability was found to be excellent and no respiratory depression was evidenced. The mean recovery time was 40 min in this noninvasive method of deep sedation.

Intranasal midazolam has also been used in doses higher than 0.3 mg/kg for children undergoing ophthalmological examination.[35] No local or general adverse reactions were observed. Midazolam is not FDA approved for intranasal administrations; however, the available literature supports its use in that fashion.

Studies of its use in conscious sedation

Although midazolam has not been recommended for children by the manufacturer, the drug has been used effectively for brief invasive procedures in children. A 0.2-mg/kg oral dose was successful in children younger than 6 years old during laceration repair.[34] IV midazolam (maximum dose 0.15 mg/kg) alone or in conjunction with an opioid offered effective sedation and amnesia during bone marrow aspirations and lumbar punctures.[17] IV midazo-

lam (0.1–0.15 mg/kg) now has replaced diazepam as the first choice sedative agent for invasive endoscopic procedures.[19] Intranasal midazolam (0.17 mg/kg) together with IM morphine allowed placement of a central venous catheter in a critically burned child.[38] It appears that midazolam may be used effectively in pediatric patients for short, slightly painful and invasive procedures. For extremely painful treatment, an analgesic drug supplement may be required. Midazolam has been used together with opioids[17,38] and ketamine[30,39] but no study has reported its use in conjunction with nitrous oxide.

Adverse reactions

The benzodiazepine group of drugs is one of the safest presently in use. Midazolam is virtually free of any side effects. The major risk associated with high doses of midazolam is hypoventilation and associated hypoxemia.[17] Respiratory depression has been reported in adults,[40] however, there have been few reports of depression in children. One reason for the numerous early reports of apnea in adults was the initial dose guidelines that underestimated the relative potency of midazolam, which is now believed to be three- to four-times more potent than diazepam—not twice as was originally thought.[19]

Respiratory depression developed in one patient who received IV midazolam and meperidine, however, it was not determined whether the complications were due to the meperidine, the midazolam, or a combination of the two drugs.[21] Another case involved respiratory arrest in a toddler who had received IV midazolam and fentanyl.[41] This complication appeared to be due to the excessive dose of fentanyl.

It is advisable to monitor children receiving midazolam for early signs of hypoventilation or apnea. Respiratory depression appears to be dose related,[6,17] and dosage regimens should be strictly followed. Some authors advise against routine use of concomitant administration of an opiate-like analgesic, which could both intensify respiratory depression[19,28] and increase the likelihood of an adverse cardiopulmonary event. However, others use the combination without complication.[17,38] In a study examining loss of consciousness in children, only one of 41 children receiving 0.4–5.0 mg/kg rectal midazolam lost consciousness (4.5 mg/kg).[27] Decreased oxygen saturation and depressed respiration were resolved with verbal stimulation, release of airway obstruction, and/or supply of positive pressure ventilation with oxygen. When given in sedative doses without any additional medications, no clinically significant respiratory depression has been reported.

An interesting report described unconsciousness associated with the use of oral midazolam (0.5 mg/kg) with IV erythromycin (400 mg) given for antibiotic prophylaxis before adenoidectomy.[42] The altered pharmacokinetics of midazolam may have resulted from reduced hepatic clearance of midazolam by the erythromycin, an enzyme-inhibiting drug. Therefore, care should be exercised when using midazolam together with erythromycin. Other less common adverse effects include: agitation, hyperactivity, combativeness, and involuntary movements.[43] No long-term adverse effect has been reported.

The relative safety of midazolam and lack of adverse effects may be attributed to the drug's selective rather than generalized CNS depressant action. The sedative effect of midazolam is related to its occupation of the benzodiazepine receptor-enhancing GABA action. This effect of midazolam can be reversed by IV administration of flumazenil (Mazicon™—Roche Laboratories of Hoffman LaRoche, Nutley, NJ),[44,45] and reversal of sedation occurs within a few minutes.[13] Due to midazolam's short half-life recurrence of sedation following reversal is not likely to occur. Routine use of flumazenil is not recommended and should be reserved for emergencies only. Although the use of flumazenil has been reported in infants, pediatric dosage recommendations have not been made.

Discussion

Midazolam offers many advantages when compared with diazepam (Table 2). It is more water soluble and, thus, when given intravenously, it is less irritating and causes fewer adverse local vascular reactions and pain. Its distribution and elimination half-lives are much shorter than with diazepam. The metabolites of diazepam are pharmacologically active while those of midazolam are not. These features facilitate the use of midazolam in a dental setting where the patient is expected to be discharged and sent home immediately after the sedation-assisted procedure. The use of sedation in a pediatric patient is always an interim method of management allowing treatment to take place. Eventually the child is expected—through various management techniques—to "graduate" and receive further dental treatment without sedation. The pediatric patient who vividly remembers dental procedures like restraints (Papoose Board®—Olympic Medical Group, Seattle, WA), administration of local anesthesia, and complicated restorative treatment may become traumatized and be reluctant to return for further treatments. The level of amnesia achieved by a sedative agent is therefore of utmost importance. It has been shown that midazolam produces anterograde amnesia more reliably and for a longer duration than diazepam.[12]

The infant or preschool child presents additional challenges to the pediatric dentist as administering a sedative

Table 2. Clinical advantages of midazolam

Water soluble
Rapid onset
Short acting
Anticonvulsant, muscle relaxant
Anterograde amnesia
Clinically inactive metabolites
Relatively high margin of safety
Reversal agent available
May be administered intranasally

agent is frequently difficult. Although the IV route is the most effective, it is not the preferred route in pediatric patients. Children generally fear injections, and the administration of an IV drug may be as traumatic to the apprehensive and anxious child as the dental treatment itself. Hence, there has been a search for effective alternate routes.

Oral administration of midazolam has many disadvantages. Midazolam has a disagreeable taste that is difficult to mask.[22] Children may refuse to swallow and may expectorate part of the drug. The clinician then is uncertain how much medication actually was ingested by the child. Oral agents tend to have a slow and variable onset and depth of sedation. They may cause nausea and have a relatively prolonged effect. In addition, oral midazolam is absorbed via the gastrointestinal tract and passes through the portal circulation decreasing bioavailability of the drug. IV doses given orally are ineffective, and triple the IV dose is required.[8,9,15]

The rectal route has been studied as an alternative to the parenteral and oral routes. This route was preferred since it was believed to be reliable, rapid, and virtually painless, but conflicting clinical results were found with this method.[27,28] Rectal absorption was found to be poor and irregular[8] and is the least reliable of all the routes studied. Furthermore, rectal administration may be uncomfortable and embarrassing for the child. Incidence of rectal pain, itching, and intraoperative defecation have been reported. Although rectal administration has been popular in Europe, it has not found favor in Great Britain or the United States and is not recommended for use in the pediatric dental setting.

Preliminary studies suggest that intranasal midazolam is an effective anxiolytic and sedative in infants and preschool children.[30-37] The rapid onset of relatively high plasma concentrations obtained after intranasal administration of midazolam offers significant advantages compared with the orally or rectally administered drug.[34] The drug is particularly useful in the dental setting, allowing administration to occur just 10 min prior to treatment. Administration is simple and relatively painless. Although intranasal administration may be objectionable, less patient cooperation is required than with oral administration in which the child must swallow the medication. Nasal midazolam is absorbed from an area rich in blood supply, avoiding the disadvantage of passing through the portal circulation, thus increasing the bioavailability of the drug. It seems that nasal midazolam has all the advantages of IV administration without the disadvantages of pain and fear associated with intravenous injections. However, additional careful study is needed before concluding that nasal midazolam is the ideal sedative agent for use by pediatric dentists. The exact mechanisms of intranasal absorption of drugs is unknown. It is speculated that these drugs may be absorbed into the brain and cerebrospinal fluid directly through the cribriform plate,[46] and some drugs may achieve proportionately higher concentrations within the brain when administered nasally than intravenously. Clinicians using this technique should proceed as cautiously as if the drug were being given intravenously.

Another relative disadvantage of the nasal administration is its dependence on the nasal mucous membrane for drug absorption, thereby permitting the common cold to be a contraindication for its use. Other possible adverse effects to the nasal mucosa caused by long-term use of midazolam or its vehicle remain to be determined.

The majority of the studies with children deal with induction into anesthesia or other examinations (echocardiographic, ophthalmologic). These procedures are relatively painless, noninvasive, of relatively short duration, and require only limited patient cooperation. In contrast, dental treatment often consists of a long procedure involving administration of local anesthetic and complicated restorative techniques necessitating total patient cooperation. The short duration of midazolam sedation is also of concern. For its incorporation into pediatric dentistry, a longer period of sedation is usually required and perhaps more than one dose will be necessary. Alternatively, a single dose may be adequate when supplemented with nitrous oxide.

All of the studies reviewed indicate the relative safety of midazolam in children regardless of its administration route. When given in sedative doses, clinically important respiratory depression does not occur. However, as with all sedative agents, children must be observed carefully and dosage regimens strictly followed whenever midazolam is used. In the unlikely occurrence of respiratory depression, a reversal agent, flumazenil, is available and is effective.

Future research should include study of the effects of intranasal midazolam together with nitrous oxide for sedation of children. In addition, the effectiveness and safety of multiple doses of intranasal midazolam for prolonged sedative effect should be investigated.

Summary

Midazolam is a short-acting, water-soluble benzodiazepine. It has anxiolytic, sedative, hypnotic, anticonvulsant, muscle-relaxant, and anterograde amnesic effects. The drug has been used as a preanesthetic sedative in adults, and more recently in children. This paper reviewed the pharmacokinetics of midazolam and its routes of administration in children. Intranasal administration was found to have many advantages including rapid onset of sedation, ease of administration, and safety. The use of intranasal midazolam together with nitrous oxide/oxygen for conscious sedation of children during dental treatment should be investigated.

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