Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients

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Abstract

The purpose of this study was to assess the effectiveness of two doses of intranasal midazolam on sedation of young children for dental treatment. Thirty uncooperative children, mean age of 32 months, who needed at least two restorative visits, participated in this study. The patients were assigned randomly to receive either 0.2 mg/kg or 0.3 mg/kg of midazolam intranasally, with the alternate regimen administered at the second appointment. All the children received 50% nitrous oxide, and were restrained in a Papoose Board® (Olympic Medical Group, Seattle, WA) with a head holder. Degree of alertness, crying, and movement were evaluated at baseline and at 5-min intervals throughout the procedure. Evaluation of overall behavior at each session was performed by one investigator, blind to the dose, using a separate rating scale. The reliability of ratings was assessed by two investigators from videotapes of the procedures. Statistical analysis showed no differences ($P > 0.05$) in the behavior of the children receiving the two doses. Successful sedation, as assessed by lack of or minimal crying and/or movement that interrupted treatment, was observed in all the treatment visits with both doses (mean score 4.66 ±1.09 for 0.3 mg and 4.40 ±1.04 for 0.2 mg). No adverse effects were observed, and all the treatments were completed successfully. (Pediatr Dent16:301–5, 1994)

Introduction

Very young children often lack cooperative ability and need to be sedated for extensive dental treatment.[1] Several sedative agents use intramuscular (IM), rectal, and oral routes.[2–6] These sedatives have significant drawbacks. Injections are painful and are known to be one of children's major fears, so this route is used less frequently in pediatric dentistry practices. Rectal administration of sedatives has been popular in Europe,[7,8] but less so in Britain and the US.[9,10] Oral premedication is by far the most popular sedative route in pediatric dentistry.[3–6] However, the onset of drugs taken orally or rectally is slow, and the recovery from oral administration is slow.[9] Children tend to spit or even regurgitate the oral medication, and many eliminate the suppository prior to its absorption. Houpt et al.[3] recommended squirting sedative solutions slowly in the back of the mouth with a syringe to allow the child to swallow, to prevent spitting, and to avoid aspiration.

Recently, the intranasal (IN) route has received a great deal of attention as a convenient and reliable alternative for drug administration. Hussain[11] observed blood levels similar to those reported following IV administration when lipophilic drugs such as propanolol were administered IN to rats, dogs, and humans. IN administration has the potential advantage of rapid absorption bypassing the first portal pass metabolism.[9]

IN administration of midazolam has been reported by several authors to be an effective premedication agent before general anesthesia.[9,12,13] Midazolam is a relatively new, potent benzodiazepine that is being used widely in medicine and dentistry. It is highly lipid soluble at physiologic pH, allowing rapid entry into the brain tissue and a rapid onset.[14] It is an effective preanesthetic medication in children when administered orally,[15–17] intravenously,[18–22] rectally,[8,10] and intranasally,[9,12,13] and has been successful intravenously for dental treatment in adults[23–26] and in children already induced with an IM dose of this drug.[27]

The ideal dose of IN midazolam for dental sedation has not yet been established. Latson et al.[28] used 0.2 mg/kg of IN midazolam for echocardiography in infants and found, "this method of sedation especially attractive in the outpatient setting." Wilton et al.[9] found no difference in the response when 0.2 mg/kg and 0.3 mg/kg of midazolam was tested for efficacy as a preoperative agent before general anesthesia in schoolchildren. Conversely, Yealy et al.,[29] in a retrospective study, found that only 27% of the patients were adequately sedated during laceration repair when 0.2 to 0.29 mg/kg of midazolam was used intranasally. They recommend a dose of 0.3 to 0.5 mg/kg for better results. The objective of this study was to assess the effectiveness of two doses of IN midazolam (0.2 and 0.3 mg/kg) for young children sedated for dental treatment.

Study method

Thirty uncooperative, young children with a mean age of 32 months (range 20–42 months) participated in this study. They were examined by a senior pediatric dentist at the Emergency Clinic of the Pediatric Dentistry, Department of the Hadassah Faculty of Dental Medicine, Jerusalem, Israel. Children who displayed uncooperative behavior (ratings 1 and 2 on the Frankl Scale) were considered for entry in the study if they were healthy (ASA 1), had no previous dental experience, and needed at least two restorative visits.[4] The

study protocol was approved by the Helsinki Committee (for human studies), and consent was obtained from one of the parents.

At the first appointment, the subjects were assigned randomly to receive either 0.2 mg/kg or 0.3 mg/kg of midazolam (Dormicum — F Hoffman-La Roche Ltd, Basel, Switzerland) intranasally; at the second appointment the alternate regimen was administered. In addition, all children received 50% nitrous oxide/oxygen analgesia.

All children were NPO for 4 hr before the appointment. The sedation agent was slowly squirted into alternating nares, with the child sitting reclined on the parent's lap. Administration of the drug was done by one of the operating dentists (SH or DR), who was blind to the midazolam dose the child had received.

All the patients were treated during the morning and similar types of treatment were planned for each of the two treatment visits.

Following IN administration of the sedative, the child remained with the parent in a quiet area for 10 min, and then was brought to the operatory with the parent, who remained in the room throughout the procedure. The child was placed in a Papoose Board® (Olympic Medical Group, Seattle, WA) with an auxiliary head rest. Vital signs were monitored with a precordial stethoscope and a pulse oximeter probe® (oxygen saturation monitor — Criticare Systems Inc., Pewaukee, WI). Pulse and oxygen saturation were recorded at the beginning of each session (baseline) and thereafter every 5 min to the end of treatment. Administration of 50% of nitrous oxide/oxygen was initiated using the rapid induction technique with a facial anesthesia mask for 2 min, after which a nasal mask was used. The treatment period was divided into two phases: the initial or preparatory phase, which included administering a local anesthetic and placing a mouth prop and rubber dam; and the treatment phase, in which the restorative procedures were performed.[4]

The degree of alertness, movement, and crying, was assessed before, during, and after the operative procedures using a rating scale described by Houpt et al.[3] (Table 1). Since the children were restrained in a Papoose Board, movement was assessed by observing the feet. Ratings during the initial or preparatory phase were recorded (usually at 10 min) and thereafter every 5 min, until the end of the procedure. The ratings during the procedure were done by one of the senior investigators (JS or AF), who also assessed the overall behavior of the child at the conclusion of each session. The evaluator was also blind to the dose the child had received. The patient's behavior was considered acceptable in one treatment session when the scores ranged from 4 to 6 and unacceptable when it was scored 1 to 3 (from a scale from 1 to 6 proposed by Houpt et al.[3] (Table 2).

The reliability of the ratings was assessed separately by two investigators (AF and JS) from videotapes of the procedures.

Each child served as his own control in a crossover design, so the main independent variable would be the dose of midazolam and the dependent variables were its effects on the behavior.

The results were submitted to statistical analysis (ANOVA and Student's *t*-test).

Results

No differences between doses were observed in the children's behavior. No adverse effects were observed, and all the treatments were completed successfully.

The mean scores for alertness are presented in Fig 1. Most of the patients were awake or slightly drowsy (scores 1.77 ± 0.48 for the 0.3 dose, and 1.59 ± 0.50 for the 0.2 dose) at baseline and for the first 30 min. These differences were not statistically significant ($P > 0.05$). At 40 min the children were drowsier when they received the higher dose (2.04 ± 0.65 for the 0.3 dose, and 1.77 ± 0.55 for the 0.2 dose). This difference was statistically significant ($P < 0.05$).

Table 1. Rating scale for crying, alertness, and movement

Score	*Crying*	*Alertness*	*Movement*
1	Hysterical crying	Fully awake, alert	Violent, interrupting teatment
2	Continuous or strong crying	Drowsy, disoriented	Continuous, making treatment difficult
3	Intermittent or mild crying	Asleep	Controllable, not interfering with treatment
4	No crying	–	No movement

Table 2. Rating scale for general behavior

Aborted	No treatment rendered	1
Poor	Treatment interruped, only partial treatment completed	2
Fair	Treatment interruped but eventually all completed	3
Good	Difficult but all treatment performed	4
Very good	Some limited crying or movement, e.g., during anesthesia or mouth prop insertion	5
Excellent	No crying or movement	6

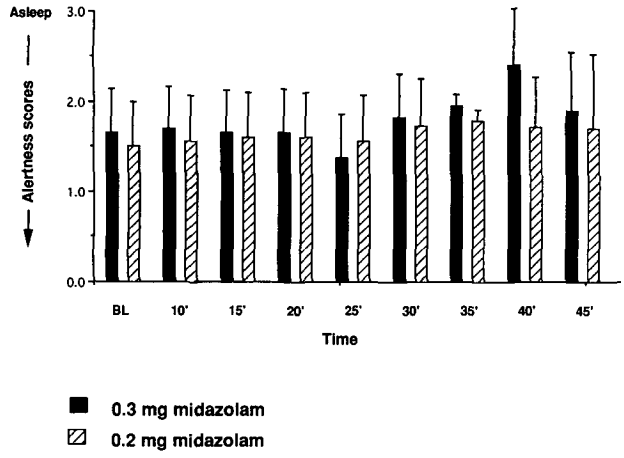

Fig 1. Mean scores for alertness.

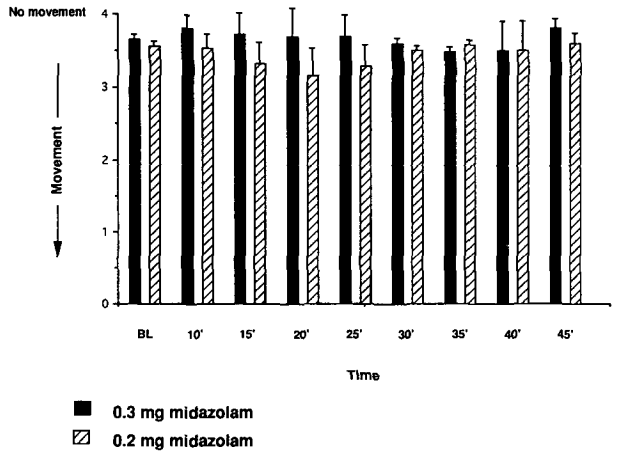

Fig 2. Mean scores for movement.

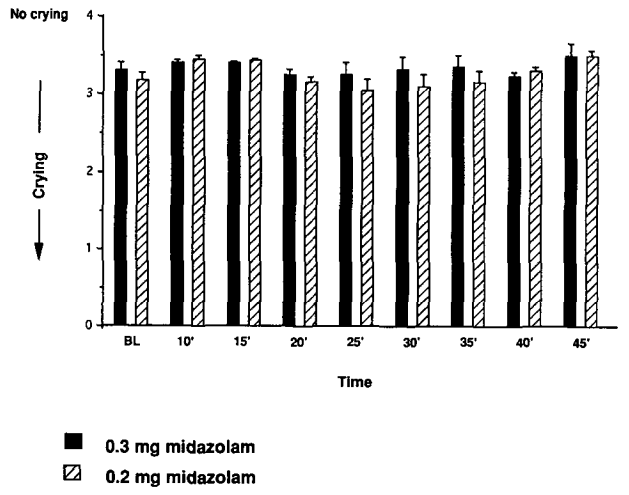

Fig 3. Mean scores for crying.

Fig 2 is the graphic representation of the mean scores for movement. In most instances, the patients presented no movement or exhibited minimum or controllable movement that did not interfere with the procedure. Only two patients made treatment difficult due to movement. However, no violent movement occurred, and all the treatment sessions were completed.

The summary of ratings for crying for all subjects is presented in Fig 3. Most children did not cry or cried mildly and intermittently, not interfering with operative procedures. Hysterical cry (score 1) was observed in only one patient for both drug regimens, persisting for the first 30 min, then becoming mild or intermittent.

The summary of overall evaluation for all subjects is illustrated in Fig 4. Successful sedation was observed in all the cases and no significant differences were observed between the two drug doses (scores 4.66 ± 1.09 for 0.3 mg/kg and 4.40 ± 1.04 for 0.2 mg/kg, $P > 0.05$).

No adverse effects (such as vomiting or allergic manifestations) were observed, and the vital signs — pulse and oxygen saturation — remained unchanged. Pulse rate increased during insertion of the mouth prop or placement of rubber dam, but quickly returned to normal when these stimuli ended. Oxygen saturation did not decrease below 95%.

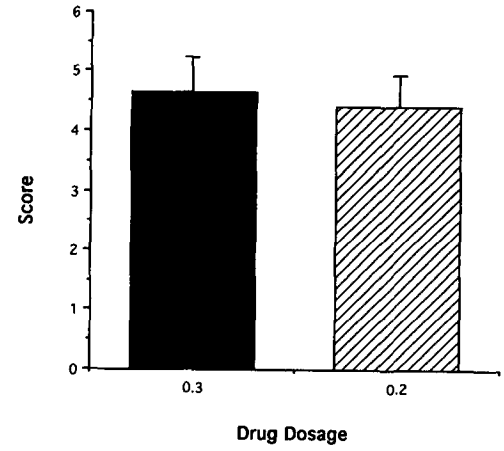

Fig 4. Mean scores for general behavior.

Discussion

Several drugs or drug combinations have been administered orally for sedation in pediatric dentistry, the most popular being chloral hydrate with or without promethazine,[3] meperidine with promethazine,[6] and hydroxyzine,[4] frequently supplemented with nitrous oxide/oxygen. Although usually evident within 30 to 45 min, clinical sedation may not occur for up to 1 hr in some children when drugs are given orally. Recently, Alfonzo-Echeverri and coworkers[5] reported a more rapid onset when oral ketamine was compared with a combination of meperidine and promethazine.

Midazolam, a relatively new benzodiazepine, has been reported to be a versatile agent for use in dentistry.[14] Although oral midazolam has not been used in dentistry, good sedation has been reported after 20–30

min in laceration repair procedures.[30] However, the dose/response relationship is not well defined, with a range of 0.2–0.75 mg/kg suggested in the literature. This range is probably the result of a significant "first pass" metabolism effect, coupled with the varying enteric absorption seen in an anxious child with a full stomach.[29]

IN midazolam had been used favorably in young children as a preanesthetic agent for surgical procedures under general anesthesia[7,12,15,20] and as a sedative for echocardiography,[28] for ophthalmological examination,[31] for endoscopy or small surgical procedures, such as the removal of foreign bodies or benign tumors,[32] for laceration repair,[29] for treating panic disorders,[33] and for dental treatment for handicapped children.[34] This is the first report of IN midazolam used to sedate healthy toddlers and preschool children requiring dental treatment.

Our data are consistent with other reports on IN midazolam[13,28–33] that document a rapid onset (10–15 min) and a short duration of effect (40–60 min). Most of the children were slightly drowsy when brought into the operatory (Fig 1), and some of them were euphoric and smiling. After 35–40 min the children became drowsier, and some fell asleep, probably due to the nitrous oxide supplementation. After 45 min, the children became more alert (lower scores), as the effect of the midazolam was probably reaching its end. This duration of sedation is well suited for dental treatment.

Walberg et al.[13] studied the pharmacokinetics of IN midazolam in children, and observed that approximately 57% of the drug was bioavailable with peak serum levels observed within 15 min. They claim that it is conceivable that IN midazolam would yield greater degrees of sedation than the plasma concentration of the drug would imply; and evidence exists that certain drugs may achieve proportionately higher concentrations within the brain or a faster onset with IN than IV administration. These compounds may be absorbed into the brain and cerebrospinal fluid directly through the cribriform plate. These authors also state that it is possible that some enteral absorption occurs after IN administration (from posterior "dripping" into the nasopharynx), but this phenomenon has not been quantified.

IN midazolam can provide sedation but not analgesia.[29] However, the mild analgesic effect of nitrous oxide/oxygen and a gentle technique for local anesthesia and placement of the rubber dam yielded minimal movement, as seen in Fig 2.

IN midazolam is not a sedative panacea for children — the overall evaluation was between good and very good, not excellent (scores 4.66 ± 1.09 and 4.40 ± 1.04). Many children cried mildly, but this did not interfere with acceptable performance of treatment. This sedation modality has several advantages:

- It enters the brain rapidly leading to a rapid onset of sedation
- It is rapidly eliminated from the body (1–4 hr, as opposed to 24–57 hr for diazepam)
- It has no active metabolites as does diazepam
- It has marked amnestic properties (children have no recall of the treatment)
- It is effective and has a high margin of safety
- It has minimal side effects; and it has cardiovascular stability.

In this study, children were ambulant and alert upon completion of the treatment and, as no instances of vomiting or allergic reaction were observed, they were dismissed after 30–45 min.

The administration of IN midazolam has two pragmatic drawbacks: this drug/route combination causes transient burning discomfort, and IN midazolam cannot be adequately employed when the child has an upper respiratory tract infection with copious nasal secretions. However, if we take into consideration all the other favorable parameters, and the fact that the maximum dose to be dispensed is 1 ml, we can conclude that 0.2 mg/kg of midazolam (as no difference was observed with 0.3 mg/kg), is an adequate sedation modality and can be recommended for dental treatment in preschool children.

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