Rectal sedation with diazepam or midazolam during extractions of traumatized primary incisors: a prospective, randomized, double-blind trial in Swedish children aged 1.5–3.5 years

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The aim of this study was to compare rectal sedation with diazepam and rectal sedation with midazolam with regard to sedative effect, treatment acceptance, and amnesia. Ninety children, 1.5–3.5 years of age, consecutively referred for extractions of traumatized primary incisors were randomly sedated with diazepam (0.7 mg/kg body weight) or midazolam (0.3 mg/kg body weight). The study design was randomized and double-blind. The level of sedation (state of mind) was assessed prior to and 10 and 60 min after administration of the drug by use of a behavioral scale (Wilton). The children's acceptance of procedures was assessed using another behavioral scale (Holst) during administration of the sedative, application of topical anesthesia, injection of a local anesthesia, and extraction. Amnesia was evaluated by the parents on the following day, with the child being asked standardized questions. Parental ratings of the child's and their own distress during and after treatment were made on a visual analog scale (VAS). No differences were found between the sedatives concerning level of sedation during treatment, acceptance of procedures, or amnesia. At discharge, 60 min after administration of the sedative, the children receiving diazepam were significantly more agitated ($P = 0.006$). Parental rating on a VAS of the child's discomfort after treatment was significantly higher in the diazepam group ($P = 0.006$). There was a tendency for children with poor acceptance of the rectal administration to display a more negative acceptance of the dental treatment. In conclusion, the present results, in combination with known pharmacological advantages, indicate that midazolam is preferable in outpatients when sedation is needed and amnesia is desirable. □ *Child behavior; dental anxiety; sedation*

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When very young children are in need of dental treatment as a result of trauma or caries, the dentist has not usually had any opportunity to instill confidence in the patient. Necessary procedures may then have to be performed under some kind of sedation. An advantage when using a benzodiazepine is the amnesic effect, which is of great value in these cases (1). Rectal sedation has been in use for many years in pediatric dentistry (2–4) and gives a fast and reliable sedative effect (5).

The prevalent medicament has been diazepam, which is now often replaced by midazolam (6, 7). With serum concentrations adequate for sedation in children, the onset of both agents is achieved in about 10 min (8, 9). Midazolam, however, has a considerably shorter elimination half-life, 2 h vs 18 h for diazepam (7). The sedative effect when administrated rectally as preanesthetic sedatives has been found similar for both agents (10). After intravenous administration in connection with endoscopy or oral surgery in adults, the amnesic effect of midazolam has been found to be greater than that of diazepam (11–13). Tolia et al. (14) reported similar amnesic effects in children for both medicaments during procedures but less recall of pain and discomfort for midazolam.

In spite of being related compounds, diazepam and midazolam are metabolized by different enzymes (15). Three percent of the Caucasian population are genetically poor metabolizers of diazepam (16) and might, hence, be affected for several days by tiredness, negative psychologic responses, and residual psychomotor impairment. A similar enzymatic deficiency has not been found for midazolam.

Although both agents may produce respiratory depression (17, 18), this effect is hardly significant in sedative doses in healthy subjects (19). During treatment, the discomfort stimulates respiration, but thereafter the child should be observed until recovery.

Since sedation is only required for a brief period, the pharmacokinetics of midazolam indicates that it might be better suited for ambulant care (20). However, the applicability to dental procedures following rectal use of midazolam vs diazepam has not been studied. Our aim was therefore to compare rectal sedation with diazepam and rectal sedation with midazolam, with regard to sedative effect, treatment acceptance, and amnesia in connection with extractions of traumatically injured primary incisors in preschool children.

Materials and methods

The subjects comprised 90 children aged 1.5–3.5 years consecutively referred to the Clinics of Specialized

Table 1. Level of sedation (state of mind) according to Wilton (1988)

Drowsy	Sitting or lying comfortably with tired or half-closed* eyes, responds to minor stimulation
Calm	Sitting or lying comfortably with open eyes, relaxed
Alert	Not clinging to parent, may whimper but not cry
Agitated	Clinging to parent and/or crying

* According to Wilton: closed eyes.

Table 2. Ratings of acceptance, according to Holst (1987)

Level of acceptance	Categories of behavior
Positive	Good cooperation
Reluctant	Reserved attitude, follows directions poorly
Negative	Crying, no cooperation
No	Active physical resistance, protests, screaming

Pediatric Dentistry in Malmö and in Halmstad, Sweden. The children were all in need of extraction of traumatically injured primary incisors. They were otherwise healthy or had only a mild systemic disease. Informed consent for the study was obtained from the parents. Non-Swedish-speaking families were not included.

The children were randomly allocated to receive diazepam (0.7 mg/kg body weight) (Apozepam, Dumex-Alpharma, Helsingborg, Sweden) or midazolam (0.3 mg/kilo body weight) (Dormicum, Roche, Stockholm, Sweden). There were 45 in each group. The medicament samples were delivered by the pharmacy in coded bottles and neither the dentist nor the parents knew which agent was being used. The treatment and behavioral ratings were performed by three specialists in pediatric dentistry, who had been calibrated before the study concerning treatment procedures, and the criteria for assessing the child's behavior had been thoroughly discussed. The kind of treatment performed is a routine treatment for the dentists involved, who have been working together for several years. The order in which the different assessments were made during the treatment is shown in Fig. 1.

Prior to rectal administration, the child's level of sedation (state of mind) was assessed according to Wilton's sedation scale (Table 1) (21). The sedative was thereafter administered with the assistance of the parents. The child's acceptance of the administration of the sedative agent was assessed according to Holst (Table 2) (22).

To evaluate the amnesic effect, a toy animal was given to the child 8 min after rectal sedation. Ten minutes after administration, the level of sedation was assessed (Wilton) and treatment begun. During treatment, the child was placed in the parent's lap to provide a sense of security. The level of acceptance was rated during application of topical anesthesia, injection of a local anesthesia (Xylocain adrenalin 2%, Astra, Södertälje, Sweden), and tooth extraction (Holst). The child remained at the clinic for 1 h after the sedative agent was administered, and the level of sedation was again assessed at discharge (Wilton).

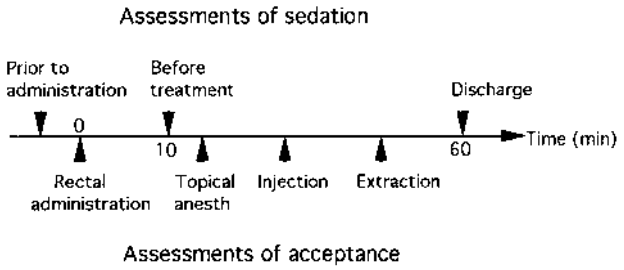

Fig. 1. The chronological order in which the different assessments were made. Assessments of the levels of sedation (according to Wilton) and acceptance (according to Holst) are shown above and below the time axes, respectively (not to scale).

The parents were given a questionnaire to fill in at home on the following day. To evaluate the presence or absence of amnesia, the parents were requested to ask their child about the dental visit and answer the following questions: 1. Does the child recall the rectal administration? 2. Does the child recall the toy animal? 3. Does the child recognize the toy animal? (from pictures showing three different animals), 4. Does the child recall the treatment? They were also asked to rate their answers to the following questions, on a 100-mm visual analog scale (VAS): 1. How great a strain was put on the child during treatment? 2. How much discomfort did the child have after treatment, the same day? 3. How much discomfort did the child have the following day? 4. How distressing was the treatment for you? The endpoints on the VAS were *no distress at all* and *very distressing*. Postoperative side effects were reported by the parents. Presence of parents' own dental apprehension was noted.

In a pilot study, the children's ability to recall events in a non-distressing situation was tested. Nine children in a day nursery aged 2.5–3.5 years were shown the same toy animal and pictures. They were all able to recall the animal on the following day and recognize it from a picture.

Wilcoxon's rank sum test (exact test using StatXact) was applied for statistical analyses concerning differences between diazepam and midazolam when the outcome variable had four distinct, ordered values, as for acceptance and level of sedation. This test was also used for analyzing the results from the VAS. Fisher's exact test was used in cases of binary answers, recall/no recall, and after dichotomization of the categories of behavior, in positive and reluctant acceptance versus negative and no acceptance. The groups were then pooled and acceptance of the rectal administration was compared with acceptance of the treatment. The study was approved by the local ethics committee at the University of Lund and the Swedish Medical Products Agency.

Results

There were 22 girls and 23 boys in each treatment group. The median age was 32 months (range 18–44) in the diazepam group and 29 months (range 15–44) in the midazolam group. No differences were found concerning

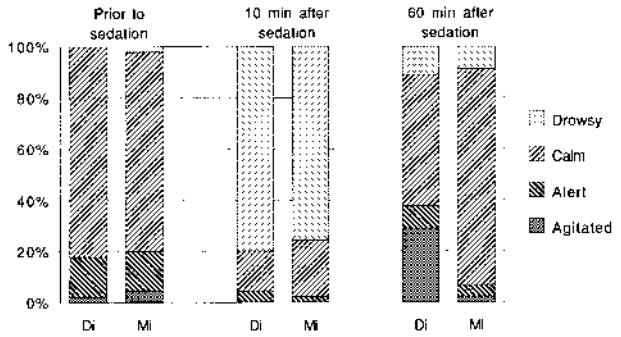

Fig. 2. Level of sedation (state of mind) (according to Wilton) assessed prior to sedation and 10 min and 60 min after rectal administration. Di = diazepam ($n = 45$), Mi = midazolam ($n = 45$). Each bar represents the entire treatment group, with proportions of different outcomes indicated.

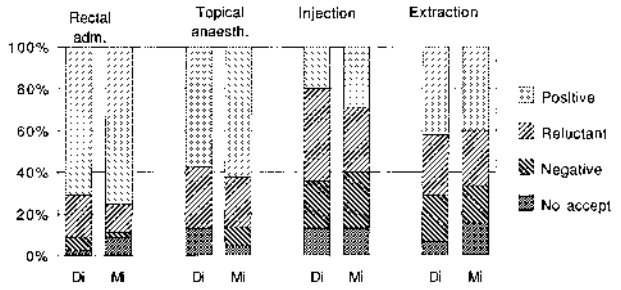

Fig. 3. Level of acceptance (according to Holst) assessed during rectal administration, application of topical anesthesia, injection of a local anesthesia, and extraction. Di = diazepam ($n = 45$), Mi = midazolam ($n = 45$). Each bar represents the entire treatment group, with proportions of different outcomes indicated.

the state of mind of the children prior to administration of the sedative (Fig. 2). Thirteen of the children who had received diazepam and 11 of those who had received midazolam had 2 teeth each extracted; the other children had 1 tooth each extracted.

Presedation assessment

In the total material, 73% had a positive and 17% a reluctant acceptance of the rectal administration of the sedative (Fig. 3). Nine children displayed either negative acceptance or no acceptance when preventive holding and active assistance from the parent was required.

Sedative effect

Ten minutes after administration of the drug no significant differences between the 2 groups were found in the level of sedation (Fig. 2). After 1 h, though, a significant difference was found: 13 children (29%) in the diazepam group were agitated compared to 1 (2%) in the midazolam group ($P = 0.006$).

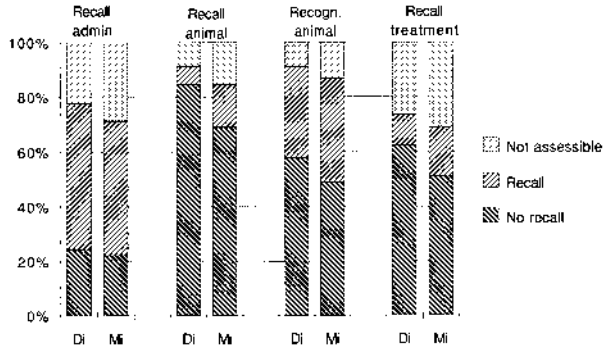

Fig. 4. Parental rating of children's recall. Recall of the rectal administration, recall of the toy animal, recognition of the toy animal, recall of the treatment. Di = diazepam ($n = 45$), Mi = midazolam ($n = 45$). Each bar represents the entire treatment group, with proportions of different responses indicated.

Acceptance of dental treatment procedures

No statistically significant differences between the groups regarding acceptance of the different procedures, application of topical anesthesia, injection of a local anesthesia, or tooth extraction were found (Fig. 3).

In the pooled group there was a tendency for children with low ratings of acceptance during the rectal administration to display more negative behavior during the dental treatment ($P = 0.07$). Of the 9 children with negative or no acceptance of the administration, 7 (78%) had negative or no acceptance during at least 1 of the procedures. Of the 81 children with positive or reluctant acceptance of the administration the corresponding figure was 33 (41%).

Questionnaire

There were no significant differences between the 2 treatment groups regarding parental report of the children's recall of the dental visit. The 4 questions could not be answered understandably by 9–31% of the children (Fig. 4). Of the children with assessable answers, 38 (93%) in the diazepam group could not recall any toy animal, and 26 (63%) did not recognize it from the pictures. In the midazolam group, the corresponding figures were 31 (82%) and 22 (56%). Among these verbal children, the parents reported amnesia concerning the treatment in 28 cases (85%) in the diazepam group and in 23 (74%) in the midazolam group. In the total material, 5 (11%) of those who received diazepam and 8 (18%) who received midazolam had partial or more pronounced memories about the treatment according to the parents. In 2 cases in the midazolam group, those memories were perceived as negative.

There was a significant difference in the parental rating on a VAS concerning the variable "discomfort after treatment, the same day". In the diazepam group the median score was 30, compared to 13 for midazolam ($P = 0.006$). The scores for the other 3 variables were comparable in both medicament groups.

According to the parents, 9 children in the diazepam group had side effects that lasted until the following day; these included aggressiveness, tiredness, and uncoordinated movements. Similar residual effects were not noted in the midazolam group, but 3 parents observed that the child was either unusually quiet or unusually lively the day after.

Four parents, 2 in each group, were not satisfied with the treatment and would prefer some other treatment regimen should the need arise again. The reasons given were aggressiveness in the child or what the parent perceived as a too painful treatment.

Discussion

Two established behavioral scales with clearly defined criteria were used to obtain reliable results. The participating operators are well acquainted with the type of assessments made in this study, since they are used routinely in daily clinical work. Acceptance of treatment and level of sedation were evaluated concordantly by all dentists and the assessments distributed in the 4 categories.

Seventy-one percent of the children in the diazepam group and 76% of those who received midazolam accepted the rectal administration without problem, which is in agreement with Coventry et al. (23), who reported an acceptance of 70% in children under the age of 5. Poor acceptance has been reported in 2.5–6% in children 2–10 years old (24, 25). In our study, poor acceptance was found in 10%, which might be because the ages of the children we studied were lower.

Sedation and acceptance

No difference in the children's acceptance of the various treatment procedures was noted between the diazepam and midazolam groups. Nor were any differences found regarding the sedative effect. Similar findings were reported by Holm-Knudsen et al. (10) in a study of the same sedatives for preanesthetic sedation. Drowsiness, which is an indication of an adequate sedative effect, was found in 76–80% in the present study. Since the pharmacodynamics of benzodiazepines is very individual (15), and it is essential to avoid oversedation among outpatients from a safety point of view, the applied doses must be within a safe range. The risk of an insufficient sedative effect is therefore always present. On this background the results of the present study might be regarded as adequate concerning levels of sedation and acceptance of treatment.

An important purpose of sedation is to prevent negative experiences of dental care for the patient, as well as for the family and the dental team. Based on previously reported high frequencies of disinhibition following rectal sedation with diazepam (26) and the much lower incidence of post-treatment agitation in the children who had been given midazolam in the present study, midazolam would be advantageous to the parents' confidence in the care given.

A good sedative effect can be counteracted by stress and is therefore not always connected with acceptance of treatment. Of the 40 children who showed negative or no acceptance during at least 1 of the treatment procedures, 98% were assessed as drowsy or calm. These findings are in accordance with Coventry et al. (23), who found that although 83% were sedated only 50% cooperated satisfactorily and that a 2-fold increase of the dose did not improve the result.

Questionnaire

No differences in amnesic effect were found between the diazepam and the midazolam groups. Earlier studies with intravenous administration in adults report a greater amnesic effect for midazolam (12, 13). In some of these studies the dose ratios were slightly different from ours, those of midazolam being proportionately higher. In children, Tolia et al. (14) reported a similar amnesic effect for both agents concerning events during endoscopy, but less recall of pain and discomfort for midazolam.

Studies of children's ability to recall are often based on the showing of pictures, or standardized procedures such as a doctor's examination (27). For the age group studied, with many children still having the retiring manners appropriate for their age, questions put by the parent rather than by an adult stranger must be assumed to be more reliable.

In a non-distressing situation, children aged 2.5–3.5 years and able to communicate can be expected to recall an event from the previous day. This was seen in the pilot study, where all the children in the day nursery recalled the toy animal they had been shown the day before and recognized it from the pictures. If retention is affected in stressful events, it would be improved (28). We found no indication that the amnesic effect would be counteracted by distress. Seventeen children were upset during at least 1 of the procedures and preventive holding from the parent was needed. The answers were non-assessable in 8 of these; in the other 9 children the parents reported treatment recall in 1 child and amnesia in 8.

Lack of amnesia could not be explained by level of sedation or by level of acceptance during treatment for any of the medicaments. All 13 children for whom the parents reported treatment recall had been assessed as adequately sedated, and 9 of them had cooperated. In the 2 children in whom the parent perceived the memories as negative, though, treatment acceptance had been poor.

In a previous study, children who had had primary incisors extracted under rectal sedation before the age of 3.5 years were followed up 2–4 years later. The parents reported persistent memories of a negative experience in 13% of the children, and they had all shown behavior management problems during dental care in the intervening period (29). Since the answers in the questionnaire in the present study in some cases were non-assessable due to deficient linguistic ability, the parental report of

negative memories in only 2 children might not truly represent the actual retention.

The VAS ratings covered a large range, stretching from 0 to almost 100 for all questions. These discrepancies were associated with neither negative acceptance by the child nor dental apprehension in the parents. In some cases the parents rated their own distress as greater than that of the child. Since this rating includes affective components, this might indicate that they found the child well cared for despite the emotionally straining situation.

Sedation usually facilitates dental treatment in small children, thereby improving the possibility of a less stressful experience for the child. This could leave a sense of ability to cope, which in some cases could enhance the child's self-esteem, especially if the parent is content with the treatment and contributes to the reinforcement of coping ability. Still, since we cannot predict which child will cooperate, amnesia is highly desirable in this type of treatment in the small child. Our previous results indicate that the amnesic effect is beneficial in helping to prevent dental fear at future dental visits (29).

In conclusion, no difference in acceptance of the various dental procedures or in amnesic effect was noted between the diazepam and midazolam groups. The children receiving midazolam were significantly more tranquil during recovery, and the child's discomfort after treatment, as reported by the parent, was significantly less for children sedated with midazolam. This, and the fact that midazolam has a shorter elimination half-life, implies that midazolam is preferable to diazepam in outpatients when sedation is needed and amnesia is desirable.

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