

**Oral Midazolam in Paediatric Dentistry: A Review**

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**Abstract**

Sedation is an important tool in getting rid of apprehension and anxiety and provides dental treatment with safety in children. Midazolam is a short-acting benzodiazepine with rapid onset of action. It has anxiolytic, muscle relaxant, and anticonvulsant activity. Within one hour of ingestion peak plasma concentration is achieved. The use of oral medication in children is usually well accepted. In various studies midazolam doses ranging from 0.2 to 1 mg/kg was used. Administration of higher oral midazolam doses (0.75 or 1.0 mg/kg) may result in a greater incidence of side effects such as loss of balance and head control, blurred vision. The need for sedation continues to grow as there is an increase in pediatric dental diseases. The increase in sedation success depends on refining the parameters and by utilizing modern drugs and routes of administration with safety measures.

**Keywords:** Oral Sedation, Conscious Sedation, Midazolam.

**Introduction**

The greatest ongoing challenge in pediatric dentistry's is safe and effective treatment of uncooperative or combative preschool children who have extensive dental needs. In today's world, parents are not comfortable with the traditional behavior management.

Thus for a safe, fast, and non-traumatic dental treatment, pharmacological behavior management is taken into consideration. <sup>1</sup>Sedation is an important tool in getting rid of apprehension and anxiety. It minimizes an uncooperative child's attempt to resist the treatment. Various routes of administration of sedation drugs like benzodiazepines are oral, inhalational, nasal, IM, subcutaneous, and IV routes. Oral route is easily accepted by both children and parents as they are usually considered as non-threatening and safe. <sup>2</sup>

Benzodiazepines such as Midazolam are a newer-generation benzodiazepine with wide toxic/therapeutic ratio and safety margin. No prolonged sedation is produced associated with other benzodiazepine such as

diazepam.<sup>2</sup> Midazolam is a short-acting benzodiazepine with rapid onset of action. It has anxiolytic, muscle relaxant, and anticonvulsant activity. It is now most widely used to generate anterograde amnesia and to stop prolonged seizures in children. Midazolam represents a convenient choice among the sedatives because of its fast onset of action and rapid termination of effect.<sup>3</sup> This paper concentrates on review of oral use of midazolam in pediatric dentistry.

### **Pharmacology**

Midazolam is a benzodiazepine derivative. It bears an imidazole ring which is fused in position 1,2 with the diazepine ring. All the characteristic effects of benzodiazepine are produced by Midazolam: 1) anticonvulsant/antiseizure action, 2) sleep-induction (Scherschlicht & Marias, 1983), 3) anti-conflict effects, 4) decrease in aggressive behaviour, 5) enhancement of presynaptic inhibition in the spinal cord, 6) decrease of the firing rate of single neurones and of the multiunit activity in specific brain areas, 7) decrease of the cyclic GMP (guanosine monophosphate) level in the cerebellum, 8) interactions with specific high-affinity binding sites for benzodiazepines.<sup>4</sup>

### **Pharmacokinetics**

In oral route midazolam is absorbed very quickly in gastrointestinal tract. Within one hour of ingestion peak plasma concentration is achieved. Because of first pass hepatic extraction only 40-50% of orally administered drug reaches the circulation in its non metabolized form. The elimination half life of oral midazolam is similar to as of intravenous administration. This indicates that the route of elimination is independent of route of administration.<sup>5</sup>

### **Metabolism**

Peak serum concentrations of midazolam are reached at different times. It depends upon the administration methods. Peaks of intramuscular and rectal routes are achieved at 15 and 30 min after administration, respectively, while the oral route attains peaks in less than 1 hr. The metabolic turn over in children is more rapid as compared to adults because children have more active liver metabolism. The elimination half-life is approx 45-60 minutes in a child. It is 2-6 hr in an adult.<sup>6</sup>

### **Oral route of administration**

The use of oral medication in children is usually well accepted. However, there are difficulties of this route of administration as well. The taste of the solution is extremely bitter which acts as a barrier that the child rejects the medication. In oral route administration measures are taken to make the midazolam drug preparation palatable and acceptable to the children. Ph of midazolam is 3.5–4.0 and thus the taste is very acidic and bitter.<sup>7</sup>

Various homemade preparations to mask the bad taste have been reported. 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. The concentrated midazolam (5 ml/mg) at 0.5 mg/kg then is mixed with 10 ml of the concentrated grape drink and refrigerated. This formulation improves the taste of parenteral preparation.<sup>6</sup>

Owing to the exaggerated response of children to needle the oral route is preferred the most for their premedication. Also the ease of distribution of medication orally is more as compared to nasal or rectal routes.<sup>8</sup>

However, there are also some disadvantages associated with the oral route, which include dependence upon patient compliance, aborting sedation if a child spits the drug out, delayed onset of drug action, inability to titrate drug dose and difficulty in administering a reversal agent or emergency drug in the absence of a patent intravenous line. Some other disadvantages of oral route are; unpredictable effect of the drug, variability in drug absorption. across the gastrointestinal mucosa and hepatic first pass effect.<sup>2</sup>

### **Pediatric Dose of Oral Midazolam**

In various studies midazolam doses ranging from 0.2 to 1 mg/kg was used. Findings by McMillan suggest that for children whose age range between 1-6 years oral midazolam in a dose between 0.5 and 1.0 mg/kg is a safe and effective premedication. However, no additional anxiolysis or sedation is achieved if dose greater than 0.5 mg/kg. In some cases it may lead to loss of balance and head control. Also dysphoria and blurred vision has been reported.<sup>9</sup> M Somri stated that 0.75 mg / kg oral midazolam appears to be the optimal oral dose in terms of effectiveness, acceptability, and safety for dental treatments in paediatric patients.<sup>10</sup> Another study concluded that 0.5 mg/kg oral midazolam appears safe and is effective in sedating most children for minor procedures.<sup>11</sup> Oral midazolam syrup is effective in producing sedation and anxiolysis at a dose of 0.25 mg/kg and infers minimum effects on respiration and oxygen saturation level even at a dose as high as 1.0 mg/kg (maximum 20 mg). However there is substantial relationship between time of onset and anxiolysis.<sup>12</sup>

### **Adverse effect of midazolam**

Midazolam is usually free of any side effects. Some studies have reported that administration of higher oral midazolam doses (0.75 or 1.0 mg/kg) may result in a

greater incidence of side effects such as loss of balance and head control, blurred vision and dysphasia as compared with placebo or 0.5 mg/kg of midazolam.<sup>9</sup> It is suggested that children should be monitored before receiving midazolam for early signs of hypoventilation or apnea. Respiratory depression appears to be dose related and dosage regimens should be strictly followed.<sup>5</sup> Decreased oxygen saturation and depressed respiration can be mostly resolved with verbal stimulation, release of airway obstruction, and/or supply of positive pressure ventilation with oxygen. No clinically significant respiratory depression has been reported when given in sedative doses without any additional medications,

### **Discussion**

Dental treatment is challenging for children of preschool age. Also the behavior management techniques fail in special children those who are mentally underdeveloped. In these cases conscious sedation has been used as pharmacological method of behavior management. This has been efficient, safe and easy to use and acceptable for patients as well as parents.

Tavassoli<sup>13</sup> compared 0.5 mg/kg oral midazolam and 0.3 mg/kg buccal midazolam. In this study an onset time of 30-45 minutes was taken for oral midazolam. It is based on the fact that the peak plasma level of oral midazolam is achieved approximately 30 minutes after drug administration. According to a randomized study done by Malinovsky<sup>14</sup> in children aged 2-5 years sedation was achieved in 13 mins with 0.5mg/kg midazolam dose. Fraone<sup>15</sup> divided children into three age groups: First (24-35 months), Second (36-47 months), and Third (47-59 months). Each child received midazolam 0.5 mg/kg orally 15 minutes before treatment. He found that oral midazolam in the dose used in this study is not sufficient in producing adequate sedation and in overcoming

strong emotional outbursts associated with dental treatment of young children whose age range is 24-60 months. This study suggests regardless of age, females demonstrated more positive behavior during treatment. Girls tended to be quieter. Also they struggled less than boys and this finding was statistically significant.<sup>15</sup>

Despite having a numerous beneficial effects, various studies have reported untoward events of side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia, and respiratory depression.<sup>16</sup> Midazolam reduced the adverse reactivity during anesthetic induction. Children who are highly anxious are the ones showing adverse reactions. Higher the baseline level of impulsivity more is the adverse reactions to anesthesia. This pattern has been observed in drug induction group not in placebo group. This suggests that midazolam may be contraindicated as a preoperative medication in children with high levels of baseline impulsivity.<sup>17</sup>

Kain et al<sup>18</sup> performed a study on children aged 2–10 yr and found that 14.1% of all children receiving oral midazolam before surgery still exhibit extreme anxiety and lack of compliance during induction of anesthesia. These children who are non-responder are younger in age and highly emotional.

The various studies conducted have used the dose ranging from 0.2 -1 mg/kg midazolam. However, these studies used extemporaneous preparations in which the IV midazolam formulation was mixed with a variety of components. Midazolam normally exists in equilibrium of both open and a closed-ring structure, the proportion of which is pH dependent. Because only the closed-ring configuration is lipophilic and physiologically active, bioavailability is sensitive to changes in pH. Therefore, the combination of the IV midazolam formulation with

diluent could alter both the absorption rate and the bioavailability.<sup>12</sup> Practitioners should be aware of one common flavoring agent that is grapefruit juice. Its use has been contraindicated with midazolam. Grapefruit juice inhibits the action of cytochrome P450 3A4 (CYP3A4). CYP3A4 is responsible for the absorption of many medications in intestine, including midazolam. Decreased absorption leads to prolonged onset time of midazolam.<sup>19</sup>

It's a challenge to provide young children with quality dental care. Pediatric dental sedation allows the practitioner to deliver the treatment in a manner that causes minimum trauma and preserves the child's trust. Also the quality and effectiveness of treatment depends upon stability of patient. Besides sedation being effective to manage pediatric anxiety, there have been untoward instances that have made this an area of suspicion. Therefore, patient selection should be done very carefully and full medical examination should be done before assigning patient for sedation. This will incorporate a culture of safety into clinical practice. The need for sedation continues to grow as there is an increase in pediatric dental diseases. Parents are also sensitive about the non-pharmacological behavior management techniques used.

The increase in sedation success depends on refining the parameters and by utilizing modern drugs and routes of administration with safety measures.

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