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The Use of Midazolam in Pediatric Dentistry: A Mini-Review

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Performing dental treatment for uncooperative child is one of the most difficult tasks for pediatric dentists. In order to deliver high quality dental care for these children, conscious sedation techniques might be required [1].

Conscious sedation techniques are methods induced by drugs producing different levels of sedation (minimal, moderate, deep). The patient retains the ability to maintain a patent airway independently and continuously as well as he is able to respond appropriately to physical stimulation and/or verbal commands [1,2].

Midazolam is one of the most commonly used medication for conscious sedation in pediatric dentistry. It presents in the market under the trade name Versed (Roche Pharmaceuticals, Nutley, NJ) [3]. It is a short-acting medication belongs to the category of benzodiazepines with average half-life of 45 - 60 minutes in children [4] in comparison to adults (2 - 6 hours) [5,6]. This contributed to the fact that children have more active liver enzymes compared to adults [4]. The body rapidly metabolizes midazolam in contrast to diazepam that takes from 24 to 57 hours to be eliminated [7].

Benzodiazepines, including midazolam, have anxiolytic and sedative properties with no analgesic effects. The pharmacological action of benzodiazepines is mediated by binding to a receptor complex named gamma-aminobutyric acid receptor (GABA receptor) enhancing the inhibitory effect of the neurotransmitter gamma-aminobutyric acid (GABA) [8]. After midazolam being absorbed from its administrative site, it is bound extensively to plasma proteins. It becomes pharmacologically active in its unbound form. Furthermore, it is metabolized in the liver by the hepatic microsomal metabolizing system (Cytochrome P-450) to compounds that are also active (alpha-hydroxymidazolam). Then, it is conjugated by glucuronic acid to form a pharmacologically inactive product that is eliminated in the urine [3,9].

Midazolam has anxiolytic, sedative, hypnotic, anticonvulsant, muscle-relaxant and anterograde amnesic effect [3]. It is 3 - 4 times more potent than diazepam with twice the affinity to benzodiazepine producing better anxyolysis and amnesia (between 75-90 % of patients will experience anterograde amnesia for up to 4 hours) [9].

Midazolam has a distinctive chemical structure that make it different from classical forms of benzodiazepine such as diazepam (Vafium Roche Laboratories of Hoffman LaRoche, Nutley, NJ). It high water solubility is accountable for its specific feature of rapid absorption and rapid metabolism [10]. Contrary to diazepam, a water-soluble salt of midazolam (pH = 3.3) could be prepared for intravenous (IV) and intramuscular (IM) administration decreasing the potential thrombophlebitis to a minimum. Once introduced in the blood (pH = 7.4), its chemical structure changes to an active which are highly lipophilic. Consequently, it will be absorbed and penetrated rapidly into the central nervous system with more rapid drug metabolism compared to the other benzodiazepine reflected as a short duration of action [9,10].

It was confirmed to be effective in conscious sedation for pediatric dental patients with large therapeutic index. However, it has common complications to be addressed. The most common complication related to midazolam involve decreased oxygen saturation, hypoventilation, laryngospasm, apnea and hypotension [8].

Routes of administration of midazolam could be intravenous (IV), intramuscular (IM), oral, rectal, sublingual, and nasal it is presented in the market in form of syrup (2 mg/ml) and injectable vials (1 mg/1ml; 5 mg/1ml). The recommended dose of midazolam in children differs per the route of administration (Table 1) [1,3,11].

Route of Administration	Dose in mg/kg
Intravenous	0.05 - 0.1; to a maximum dose of 10 mg.
Intramuscular	0.1 - 0.15; to a maximum dose of 10 mg.
Oral	0.25 - 0.75; 15 - 30 minutes before the intervention, to a maximum single dose of 20 mg.
Rectal	0.4 - 1.0
Sublingual	0.2 - 0.5
Nasal*	0.2 - 0.3; 10 - 15 minutes before the intervention.

Table 1: *Common Pediatric Dosed of Midazolam Based on the Route of Administration.*

** Repeat dose after 10 minutes if needed.*

Several studies investigated the effects of different routes of administration on the efficacy of midazolam. Some studies showed that no significant difference was found between different routes of administration for midazolam. Kogan and colleagues conducted a randomized double-blind study investigating the efficacy of midazolam in four different routes of administration. It demonstrated that intranasal, oral, rectal, and sublingual administration of midazolam offers good level of sedation and anxyolysis by which most the children presented easiness for mask placement for inhalation induction (more than 75% of children). Average sedation and anxiolysis increased with time. Intranasal administration achieves a maximum level of sedation and anxyolysis at 20 minutes compared to other routes of administration where a maximum level was accomplished at 30 minutes. Intranasal route produces faster impact; however, it accompanies with considerable nasal irritation [12]. Taking in consideration that children were not crying before drug administration, the frequency and duration of crying was greater following intranasal compared with sublingual administration (71% vs. 18% ($P < 0.0001$) and 48 +/- 56 vs. 25 +/- 49 s ($P = 0.004$), respectively) [13]. Intranasal midazolam is an excellent alternative for rapid premedication provided that respiratory monitoring is used [14].

However, in another study investigated the effect of midazolam in three different transmucosal routes of administration (nasal, rectal, sublingual) in children, the results were contrast. A statistically significant difference in the midazolam level 30 minutes after administration was found between the nasal and sublingual groups. The sublingual group was statistically higher. Meanwhile, the psychological parameters (e.g., emotional situation, shivering, awareness, respiratory rate and facial color) in all three groups was significantly changed after 10 minutes of administration. These parameters did not significantly differ between the three groups throughout the study [15]. Sublingual administration of midazolam was found to be easily taken with highest plasma level and lowest deviations. Therefore, it might be the first choice in children [13,15].

In a study conducted by Malinovsky and colleagues investigating the effect of intranasal, rectal and oral routes on plasma midazolam concentrations. Intranasal route of administration for midazolam produces the fastest sedation which was described to be adequate (7.7, SD 2.4 min) followed by oral (12.5, SD 4.9 min). Rectal route was found to produce adequate sedation lately (16.3, SD 4.2 min) [14].

Since long time ago, midazolam was only available as injectable form. This form has been used orally despite its extremely bitter taste. Flavoring agents have been added to this form to enhance the taste and facilitate its oral administration. Examples of flavoring agents mixed with the injectable midazolam include pharmacy prescribed flavorings such as Ora-Sweet (Paddock Laboratories, Minneapolis, MN, NDC #0574-0304-16), Acetaminophen elixir (Pharmaceutical Associates, Greenville, SC), presweetened Kool-Aid (Kraft General Foods), citrus juices including grapefruit juice [11,16,17]. Interestingly, Grapefruit juice in contrast to other citrus juices, is contraindicated to be

used as a flavoring agent with midazolam. It is found to inhibit cytochrome P450 (CYP) 3A4. CYP 3A4 is found in the intestine and liver. Inhibition of this cytochrome results in delayed absorption and reduced first pass effect on midazolam. This results in increased blood plasma levels of midazolam of 56% and increased midazolam bioavailability of 35% causing excessive level of sedation in children [11].

Finally, Midazolam continues to be used frequently in pediatric dentistry. It is suitable for short invasive procedures including dental treatment for uncooperative children. Despite that midazolam is safe and effective sedative, it has to be conducted by health care provider that are well-practiced in the field of conscious sedation in a facility providing monitoring and support for respiratory and cardiovascular functions. The ability of recognition and management of complications associated with sedation should be managed properly and immediately to save patient's life.

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