USE OF ORAL MIDAZOLAM SEDATION IN PEDIATRIC DENTISTRY: A REVIEW

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ABSTRACT

Most fearful and uncooperative children can be managed with behavioral management techniques. However, when behavioral management strategies fail, some form of pharmacologic sedation or anesthesia has to be utilized. Midazolam, one of the commonly used oral sedation agent in children has several characteristics such as safety of use, rapid onset and some degree of amnesia that makes it a desirable sedation agent in children. Therefore, oral midazolam sedation is recommended for short dental procedures in children. This review paper discusses various aspects of oral midazolam sedation including, advantages of oral route of sedation, pharmacokinetics of midazolam, range of oral dose, midazolam antagonist, and clinical procedure. The paper also includes general guidelines for sedation. The need for appropriate training (for personnel) in sedation, provision of appropriate equipment/monitoring devices and presence of rescue mechanisms is also emphasized.

Key Words: Oral midazolam, sedation, children, dental treatment.

INTRODUCTION

Dental management of children with behavioral problems remains a major challenge to dentists. The behavioral problems are usually encountered in children younger than six years of age due to factors such as immature reasoning, limited coping skills and anxiety/fear resulting from lack of experience. Provision of successful dental treatment in anxious/fearful children is largely dependent upon successfully gaining their cooperation. Technical skills are of a little value unless the child cooperates. Use of sedation can be very helpful in allaying apprehension and minimizing an uncooperative child’s attempt to resist treatment.

Sedation drugs are administered through various routes such as oral, inhalational, nasal, intramuscular, subcutaneous, and intravenous routes. All these routes have certain advantages and disadvantages. Oral route is complicated by variable absorption level of sedation drug in gastrointestinal tract and inability of the operator to titrate the drug dose to the desired effect. However, orally administered sedatives are well accepted by most children, and are usually perceived as non-threatening.

A variety of sedative drugs has been used for oral sedation in young children including benzodiazepines. Midazolam is a newer-generation benzodiazepine with wide toxic/therapeutic ratio and safety margin, and does not produce prolonged sedation associated with other benzodiazepine such as diazepam. When taken orally, midazolam is rapidly absorbed in the gastrointestinal tract, produces its peak effect in relatively shorter time of about 30 minutes, and has a short half-life of about 1.75 hours. When given in doses between 0.5 to 0.75 mg/kg of body weight, oral midazolam has been found to be a useful sedative agent for pediatric dental outpatients. Midazolam has also been shown to enhance anterograde amnesia when used preoperatively in pediatric patients. Midazolam is a short acting anxiolytic agent, with short duration of action, that makes its use limited to short dental procedures only.

It is of utmost importance to remember that any type of sedation carry a risk of untoward effects. The

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practitioner and support personnel should be sufficiently trained, and the place must be adequately equipped before any form of dental sedation is administered, including minimal oral sedation. The American Academy of Pediatric Dentistry “Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures” provide basic information on dental sedation in children. The readers are strongly encouraged to read and consult other relevant text and guidelines, and attend training courses before using any form of dental sedation.

DENTAL SEDATION

The American Society of Anesthesiology updated the sedation terminology and definitions in 1999, and The American Academy of Pediatric Dentistry has also listed the following three levels of sedation.

Minimal Sedation (Old Terminology: Anxiolysis): A drug induced state during which patients respond normally to verbal command. Although cognitive function and coordination may somewhat be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate Sedation (Old Terminology: Conscious Sedation or Sedation/Analgesia): A drug-induced depression of consciousness during which patients respond purposefully to verbal commands (e.g., “open your eyes” either alone or accompanied by light tactile stimulation - a light tap on the shoulder or face, not a sternal rub). For older patients, this level of sedation implies an interactive state; for younger patients, age-appropriate behaviors (e.g., crying) occur and are expected. Reflex withdrawal, although a normal response to a painful stimulus, is not considered as the only age-appropriate purposeful response (e.g., it must be accompanied by another response, such as pushing away the painful stimulus so as to confirm a higher cognitive function). With moderate sedation, no intervention is required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. However, in the case of procedures that may themselves cause airway obstruction (e.g., dental or endoscopic), the practitioner must recognize an obstruction and assist the patient in opening the airway. If the patient is not making spontaneous efforts to open his/her airway to relieve the obstruction, then the patient should be considered as deeply sedated.

Deep Sedation (Old Terminology: Deep Sedation/Analgesia): A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully (see discussion of reflex withdrawal above) after repeated verbal or painful stimulation (e.g., purposefully pushing away the noxious stimuli). The ability to maintain ventilatory function independently may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. A state of deep sedation may be accompanied by partial or complete loss of protective airway reflexes.

ORAL ROUTE OF SEDATION

The oral route is the oldest and most economical of all routes of drug administration. It is also the most universally accepted and easiest method. Most practitioners prefer the oral route of drug administration due to high safety, minimal complications and usually easy acceptance by children. In addition, parents also prefer this less invasive method of drug administration. Other advantages of oral drug administration are; no specialized training required, minimum equipment utilized and low incidence of adverse reactions. From the patients’ point of view, the main advantage of the oral route is avoidance of an injection with its inherent risks and psychological effects. Patients also prefer the oral route over parenteral routes because of discomfort/pain associated with venipuncture or intramuscular administration. Therefore, oral sedation is probably the most widespread form of sedation used in dentistry. However, there are also some disadvantages associated with the oral route, which include dependence upon patient compliance, aborting sedation if a child splashes 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.
Absorption of drug is affected by the presence of food in the stomach, and the drug is subjected to ‘first-pass’ liver metabolism before reaching the general circulation, thus varying the depth and duration of action. After oral administration of a sedative agent, the primary absorption of most drugs takes place from small intestine. Therefore, it is important to get the drug from the stomach into the small intestine as rapidly as possible. The time required for a substance to be expelled from the stomach is called “gastric emptying time”. The presence of food in the stomach will decrease the absorption of drugs into the systemic circulation by increasing gastric emptying time, and if the drug gets bound to the food, it becomes unavailable for absorption. Anxiety itself may delay gastric emptying and therefore delay absorption and onset of action. It is therefore recommended that oral sedation medications be administered in the absence of food and, the traditional psychological behavior management techniques be utilized before and during oral drug administration to decrease the anxiety. 18, 21

Once absorbed from the stomach or small intestine, drugs enter the hepatic portal system, allowing exposure to liver enzymes, which may metabolize a percentage of the drug. The extent of this action is drug specific and is known as the “hepatic first-pass” effect. 18, 21 After leaving the liver, orally administered drugs reach the systemic circulation in non-metabolized form. The portion of an administered dose that reaches the systemic circulation in active form is available for distribution to target tissue(s) is termed as “Bioavailability”. 22

**BENZODIAZEPINES**

The term “benzodiazepine” refers to the common chemical structure shared by all of the compounds within this class of drugs. The site of action for benzodiazepines are specific receptors in the central nervous system (CNS) associated with GABA receptors. Benzodiazepine receptors have been identified in different body tissues including the heart and skeletal muscles, though the predominance appears to be in the central nervous system. 23 The low incidence of respiratory depression with benzodiazepines may be related to the low density of binding sites in the brain stem. 24

Midazolam has a high affinity for the benzodiazepine receptor in central nervous system; in-vitro data demonstrating approximately twice the affinity as compared to diazepam. 25, 26

**Advantages of Benzodiazepines**

Benzodiazepines have been widely used for premedication. 27, 28 Principal advantages of this class are their relative safety, availability of antagonist, selective anxiolytic activity and ability to produce anterograde amnesia. The relative safety is due to the high therapeutic index. The high therapeutic window implies that there is a great difference in the level of dose between desired responses and that which can cause side-effects. 22

In addition to the anxiolytic, sedative, and amnestic effects, benzodiazepines may indirectly elevate the patient’s threshold for pain. This does not mean that they are analgesics, but the patient appears to reach a state of mental indifference. In this altered state, many patients are less perturbed by mild noxious stimulation that might otherwise be distressing. 22 Compared with other central nervous system (CNS) depressant such as barbiturates and opioids, benzodiazepines have minimal influence on respiration and cardiovascular function. 22

The adverse effects profile of benzodiazepines is minimal. Excessive CNS depression and respiratory depression occur only in overdose situations. Excessive CNS depression usually manifest as severe alterations in consciousness, ranging from weak or inappropriate responses to verbal command or stimulation to the loss of consciousness. Depression of respiration that requires intervention is an indication that an overdose has occurred. Careful selection of the benzodiazepines dose decreases the likelihood of these adverse effects. 29

**Diazepam**

The properties of diazepam include strong anti-anxiety effects but minimal somnolence and virtually no amnesia at orally prescribed doses. Diazepam has long-acting metabolites (oxazepam and desmethyldiazepam) that have sedative properties. Consequently, the clinical duration of diazepam sedation tends to be moderate to long in length. Diazepam readily redistributes into lipid structures, and a clinical rebound effect can occur when this sequestered
drug is re-released into the bloodstream after a meal. It is common for patients who have been sedated earlier to get drowsy after eating, and so they need to be warned of this possibility.29

Midazolam

A high water solubility of midazolam as compared with diazepam is the major advantage of midazolam. Midazolam belongs to a new class of benzodiazepines called Imidazobenzodiazepines.30 This class also includes the receptor antagonist flumazenil.31 The increased water solubility allows midazolam to be packaged without diluents, thus decreasing venous irritation and dysrhythmias.30,32 The pharmacological actions of midazolam are identical to those of other benzodiazepines including anxiolytics, sedation and amnesia.12

PHARMACOKINETICS OF MIDAZOLAM

Absorption

Midazolam is rapidly absorbed from the gastrointestinal tract following oral administration.25 Drowsiness has been noticed 15 minutes after an oral dose, with peak effects within 30-90 minutes.32 Due to liver first-pass metabolism, only 40-50% of orally administered dose reaches the systemic circulation. Parenteral routes of administration result in higher bioavailability and rapid onset times.

Distribution

Midazolam has a volume of distribution (Vd) of 1-2.5 L/kg in normal healthy individuals.25,30 Obese patients have an increased Vd because of enhanced distribution to peripheral adipose tissues.25,30 Midazolam is extensively bound to plasma proteins primarily albumin with a free fraction representing only 4% of a given dose.25 The pharmacological effect of midazolam ranges from one to four hours. The duration of effect is determined primarily by the rate of movement from the central to the peripheral compartment.32 Midazolam has a short distribution half-life of several minutes because of fast tissue uptake.30 Return to baseline values for objective neurological tests is reported 1.5 hour after intravenous injection and 2 hours after oral administration.23

Metabolism

Midazolam, like other benzodiazepines is biotransformed by hepatic microsomal oxidation followed by a glucuronide conjugation.30 Initially, Midazolam is hydroxylated by Cytochrome P450-3A4 to its primary metabolite, alphahydroxy-midazolam, and minimally to inactive metabolites. These metabolites are then excreted in urine as glucuronide conjugates.34 Alphahydroxy-midazolam is pharmacologically active and has sedative properties equivalent to midazolam. This major metabolite is produced in higher concentrations following oral administration as a result of first-pass metabolism. Plasma clearance of midazolam is greater in supine patients because of 40-60% increase in hepatic blood flow during supination.32

Elimination

Midazolam has a short elimination half-life of 1.5-3.0 hours compared with more than 20 hours of diazepam.35 However, the pharmacological duration of action is generally only 60-120 minutes.36 Plasma clearance of midazolam is 5.8-9.0 ml/min/kg in healthy individuals but is decreased in elderly individuals.33 Almost 90% of an orally administered dose of radiolabeled midazolam is excreted within 24 hours.25 The major route of elimination is kidney, with less than 10% excreted in the faeces within 5 day.25 Midazolam has been associated with accumulation and prolonged sedation in patients with renal dysfunction.34,37

Pharmacodynamics

Midazolam has anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic and amnesic properties.12,25 At higher dose, midazolam may produce respiratory depression. There are no effects of midazolam reported on cardiovascular system when used alone.38

ORAL MIDAZOLAM SEDATION

The clinical use of midazolam is primarily reserved as premedication/sedation drug, though it also has anticonvulsant and muscle relaxant properties. One of the limiting factors in the use of midazolam for sedation is the short length of action.30 So, midazolam can be used effectively in pediatric patients for short, mildly painful and minimally invasive procedures.40
Use of Oral Midazolam Sedation in Pediatric Dentistry: A Review

**Pediatric Dose of Oral Midazolam**

Midazolam has been used orally at doses between 0.2-1.0 mg/kg with onset of action between 20-30 minutes.12,41,42 Several studies have been conducted to determine an optimal dose of oral midazolam for sedation by comparing various doses of oral midazolam. Singh et al41 found that oral midazolam in a dose of 0.5 mg/kg is suitable premedication for child patients (ASA Category I) during short dental procedures. Another study compared two dosages of oral midazolam (0.3 mg/kg or 0.5 mg/kg) in 31 physically and neurologically compromised pediatric (3-18 years) dental patients; both dosages proved successful, without intraoperative or postoperative complications.43 Fraone et al44 evaluated the effect of orally administered midazolam with a dose of 0.5mg/kg in three age groups: group I (24-35 months) group II (36-47 months) and group III (47-59 months), with conclusion that there were no significant clinical differences among the three groups. On the other hand, Saarnivaara et al45 recommended oral midazolam dose of 0.5 mg/kg for children less than five years and 0.4 mg/kg for older children. Ma et al7 concluded that oral midazolam in the doses between 0.5 – 1.0 mg/kg can be a safe and acceptable sedation drug especially in children over 3 years of age. Somri et al46 compared three doses of oral midazolam, between 0.5 to 1.0 mg/kg in 3-10 year old children, with conclusion that 0.75 mg/kg appears to be the optimal dose in terms of effectiveness and safety. The preceding studies especially the more recent ones establish the efficacy of oral midazolam doses between 0.5 mg/kg to 0.75 mg/kg as sedative agent to manage apprehensive pediatric dental patients.

**Side Effects of Midazolam**

Midazolam is virtually free of any serious side effects when given in recommended oral doses. The major risk associated with high doses of midazolam is hypventilation and associated hypoxemia.39 Respiratory depression has been reported in adults,47 however, there have been few reports of respiratory depression in children. One reason for the numerous early reports of apnea in adults was the old dose guideline 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).48 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.49 Similarly, Dionne50 reported that oral midazolam at doses of 0.75 to 1.0 mg/kg produced a higher incidence of side effects and decreased respiration manifesting as oxygen saturation values below 80% in some children. On the other hand, many studies reported that oral midazolam is safe and effective sedative agent at doses of 0.5mg - 1.0mg/kg.1,6,7,46 Litman et al51 reported that the use of 0.7mg/kg oral midazolam did not result in clinical respiratory depression nor upper airway obstruction, though in some children caused an increased level of sedation beyond minimal sedation.

It is advisable to monitor children receiving midazolam for early signs of hypoventilation or apnea. Respiratory depression appears to be dose related and dosage regimens should be strictly followed.25,39 Some authors advise against routine use of concomitant administration of an opiate-like analgesic, which could both intensify respiratory depression and increase the likelihood of an adverse cardiopulmonary event.48 However, others have used the combination without complication.39,52 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. When given in sedative doses without any additional medications, no clinically significant respiratory depression has been reported.

**Drug Interactions**

Midazolam is metabolized in the liver by the cytochrome P450 oxidase system. Cimetidine, a cytochrome P450 oxidase system inhibitor, increases the mean steadystate concentration of midazolam by as much as 80%.53 In individuals pretreated with either cimetidine or ranitidine the bioavailability of midazolam increased by approximately 30%.54 Midazolam often has an earlier onset of action and increased sedation in individuals pretreated with an H2 receptor antagonist. Omeprazole may also inhibit the oxidative metabolism of midazolam.55 Macrolide antibiotics are also known cytochrome P450 enzyme in-
hbitors. Conversely, rifampin acts as a cytochrome P450 enzyme inducer and may enhance the clearance of midazolam.56 Erythromycin reduces the clearance of oral and intravenous midazolam and increase its half-life.57 Oral contraceptives (for adult patients) prolong the elimination half-life of diazepam and may inhibit the metabolism of midazolam by a similar mechanism.58

**Anterograde Amnesia**

Anterograde amnesia is a lack of recall of events occurring from the time of administration of a drug onwards. This is to be distinguished from retrograde amnesia, which is a lack of recall of events occurring before the drugs administration. Midazolam affects memory process by impairing the ability to acquire new information.9,59 The amnesic effect of midazolam appears to be independent of the sedation quality. Midazolam produces anterograde amnesia and may indirectly enhance the retention of material learned before treatment as consequence of the reduced learning of information presented after the drug takes effect. The amnesia achieved with midazolam has been shown to be greater than that seen with diazepam.60 The amnesic effect of midazolam generally persists for 20 to 30 minutes.61

**Flumazenil: A Midazolam Antagonist**

Flumazenil is an imidazobenzodiazepine derivative that antagonizes the action of benzodiazepine on the central nervous system. The safety of midazolam sedation has been significantly improved by availability of flumazenil. Previous studies investigating the efficacy of flumazenil have demonstrated significantly shorter recovery times, increased patient alertness and consequently earlier discharge home.62 For the reversal of the sedative effects of benzodiazepines administered for conscious sedation in pediatric patients older than one year of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered intravenously over 15 seconds. In case the desired level of consciousness is not gained within 45 seconds, further injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60 seconds intervals where necessary up to a maximum of 4 additional times to achieve full consciousness and normal cardiorespiratory function.63

**Oral Midazolam with Nitrous Oxide**

Oral midazolam is often used in combination with nitrous oxide for dental sedation in children. A study by Pisalchaiyong et al64 compared the effectiveness of oral diazepam and midazolam alone and in combination with nitrous oxide for sedating autistic patients during dental treatment; the midazolam/nitrous oxide combination was found significantly more effective than diazepam/nitrous oxide combination. A study by Al-Zahrani et al4 reported that combination of oral midazolam (0.6mg/kg) and nitrous oxide (30-50%) is effective and safe in young dental patients who need minimal restorative treatment. Ozen et al8 have also recently reported similar results with combination of 0.5 mg/kg oral midazolam and nitrous oxide (50%) in 4-6 year old children. The use of nitrous oxide may prolong the working time to some extent and simultaneously incorporates its own desirable effects (such as analgesia) in the clinical situation.

Midazolam has also been used in combination with various other sedatives. Review of literature on use of various drug combinations is beyond the scope of this review. However, it is strongly emphasized that combining two or more of these drugs enhances the sedative effects of each of these substances, increasing the risk of respiratory depression and overdose. The sedationist must have knowledge and training in using these drug combinations and management of any possible untoward effects.

**CLINICAL PROCEDURE**

**Patients Selection**

Healthy patients (ASA 1 Category – Table 1)65 between the age of 4-12 years, and in Behavior Category of Frankle Scale 2 (Table 2)66 needing short dental procedures are normally selected for oral midazolam sedation. Experienced operators, in selected patients can perform more invasive dental treatment including extractions with midazolam oral sedation. Utmost care has to be taken in patient selection to avoid any medical complication during and after sedation. Patients who have recently used medications such as erythromycin or anticonvulsants that may have interference with pharmacokinetics of midazolam are not selected for midazolam sedation.
**Pre-sedation Appointment**

The patients who are suitable for oral midazolam are appointed for confirmation of medical/dental status and clinical/radiographic examinations. Full verbal and written explanation is provided to parents regarding the sedation procedure, type of medication that will be used with its safety and side effects. The reason to select midazolam and other option of treatment including advantages and disadvantages of each technique are also explained. A written consent is obtained from parents for sedation of their child. The consent forms are designed per ethical and legal requirements in area of the practitioner. Preoperative instructions (both verbal and written) are provided to the parents, including nothing per mouth at least 6 hours before the appointment (Table 3)\(^\text{15}\). They are advised to call for cancellation if the child gets ill (flu, cough, fever etc).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
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</tr>
<tr>
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<td>A patient with mild systemic disease</td>
</tr>
<tr>
<td>Class 3</td>
<td>A patient with severe systemic disease</td>
</tr>
<tr>
<td>Class 4</td>
<td>A patient with severe systemic disease that is a constant threat to life</td>
</tr>
<tr>
<td>Class 5</td>
<td>A moribund patient who is not expected to survive without operation</td>
</tr>
<tr>
<td>Class 6</td>
<td>A declared brain-dead patient whose organs are being removed for donor purposes</td>
</tr>
</tbody>
</table>

### TABLE 1: THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) PHYSICAL STATUS CLASSIFICATION\(^\text{65}\)

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### TABLE 2: FRANKL BEHAVIORAL RATING SCALE\(^\text{66}\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Frankl Behavioral Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rating 1</td>
<td>Definitely negative: Child refuse treatment, cries forcefully, fearfully, or display any overt evidence of extreme negativism.</td>
</tr>
<tr>
<td>Rating 2</td>
<td>Negative: Reluctant to accept treatment and some evidence of negative attitude (not profound).</td>
</tr>
<tr>
<td>Rating 3</td>
<td>Positive: The child accepts treatment but may be cautious. The child is welling to comply with the dentist, but may have some reservations.</td>
</tr>
<tr>
<td>Rating 4</td>
<td>Definitely negative: This child has a good rapport with the dentist and is interested in the dental treatment.</td>
</tr>
</tbody>
</table>

### TABLE 3: APPROPRIATE INTAKE OF FOOD AND LIQUIDS BEFORE ELECTIVE SEDATION\(^\text{15}\)

<table>
<thead>
<tr>
<th>Ingested Material</th>
<th>Minimum Fasting Period (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear liquids: water, fruit juices without pulp, carbonated beverages, clear tea, black coffee</td>
<td>2</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4</td>
</tr>
<tr>
<td>Infant formula</td>
<td>6</td>
</tr>
<tr>
<td>Nonhuman milk: because nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period</td>
<td>6</td>
</tr>
<tr>
<td>Light meal: a light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.</td>
<td>6</td>
</tr>
</tbody>
</table>

### TABLE 4: PATIENT’S DISCHARGE CRITERIA\(^\text{72}\)

- The patient is able to response to his or her name
- Respond to touching or shaking his/her hand
- Ability to maintain a standing posture
- Absence of dizziness or disorientation
- Acceptable vital signs (close to base-line)

Medications

Midazolam has a disagreeable taste that is difficult to mask.\(^\text{67}\) Children may refuse to swallow it, and expectorate whole or part of the drug. The clinician then becomes uncertain about how much medication has actually been ingested by the child. Various homemade preparations to mask the bad taste have been suggested.\(^\text{67,69}\) An oral midazolam syrup was used by...
AlZahrani et al in their study of oral midazolam pediatric dental sedation; with no case of drug expec- toration during their study. The syrup is prepared in a concentration of 2mg/ml with stability of 30 days if kept refrigerated. The mixture consists of intravenous midazolam (ampoules of Dormicum® 15 mg/3ml, F. Hoffinan - La Roche Ltd, Basel, Switzerland). The dilution of Dormicum ampoules is carried out by using dye-free flavoured syrup. The diluents consist of sorbitol 45g, sucrose 15g, saccharine 0.2g, sodium benzoate 0.15g, citric acid 2g in 100ml of distilled water. Then 45ml of diluents syrup and 30ml of intravenous midazolam (10 ampoules x 3ml which contain 10x15mg = 150mg midazolam) are mixed. The final preparation has midazolam 2mg/ml.

**Sedation Protocol**

The child is first examined on the day of sedation for medical clearance. Then the patient’s weight is taken by electronic weight scale. Baseline blood pressure, heart rate, and oxygen saturation are recorded. The dose of midazolam is calculated for the child and then the syrup given to the child in a cup with the assistance of his/her parents. The appointment is postponed if the child expectorates whole or part of the drug. The child then waits in a quiet room with his/her parents, and signs of onset of sedation are observed every 5 minutes after drug administration. The following signs are observed in determination of onset of sedation:10

- Glazed look
- Delayed eye movement
- Lack of muscle coordination
- Slurred speech
- Sleep

As the above signs are observed after the drug administration, the patient is then moved to the operating room/surgery carried by his/her parent. In the operating room; pulse oximeter clip (Vitalmax 800 Monitoring Equipment: Pace Tech. Inc., Clearwater, FL 34615) is attached to the child’s big toe of right foot. The blood pressure cuff is attached to left arm by a trained assistant and the patient is immobilized for his/her safety using a papoose board (Olympic, Medical Group, Seattle, WA).

A mouth prop (scissor type) is placed in the side of the mouth not being treated. Then, topical anesthesia is applied for 2 minutes followed by appropriate local anesthesia (2% lidocaine with epinephrine 1:100,000). Rubber dam is applied when needed and the required restorative treatment accomplished.

All hemodynamic parameters are monitored during the course of the treatment. At the end of dental procedures, hemodynamic parameters are again recorded and the child then transferred to quite room and monitored for recovery. The child is discharged when he/she fulfills the discharge criteria (Table 4). Before the discharge, hemodynamic parameters are again recorded. Post-sedation instructions (both verbal and written) are given to the parents. Parents are instructed to give juice only after two hours from discharge and give slowly to avoid vomiting. Parents are advised to observe the child for rest of the day. They must not allow the child to play with sharp objects or walk on stairs alone. The parents are provided with a telephone number in case of any problem.

The following physiological parameters are recorded at base line, during, after and at discharge:

- Heart rate (HR)
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Oxygen saturation (SaO 2%)

Tachycardia and hypertension are considered if there was an increase in heart rate and blood pressure respectively more than 20% from baseline value. If the heart rate and blood pressure decreased more than 20% from baseline, it is considered as bradycardia and hypotension respectively. Hypoxemia is evaluated based on pulse oximeter recordings. Oxygen saturation from 95% or above is considered normal. Any reading less than 95% is recorded.

**Evaluation of the Drug Side Effect**

The patient is observed in the recovery room for any side effect such as nausea, vomiting. The side effects may also be evaluated by asking the parents or the child’s guardian through telephone.

**GENERAL GUIDELINES FOR SEDATION**

The American Academy of Pediatric Dentistry has provided following guidelines for pediatric dental sedation.15
Use of Oral Midazolam Sedation in Pediatric Dentistry: A Review

Candidates

Patients who are in ASA I category are considered appropriate candidates for minimal sedation. Practitioners are encouraged to consult with appropriate specialists and/or an anesthesiologist for patients suspected of increased risk of experiencing adverse sedation events.

Facilities

The practitioner who uses sedation must have immediately available facilities, personnel, and equipment to manage emergency and rescue situations. The most common serious complications of sedation involve compromise of the airway or depressed respirations resulting in airway obstruction, hypoventilation, hypoxemia, and apnea. Hypotension and cardiopulmonary arrest may occur, usually from inadequate recognition and treatment of respiratory compromise. Other rare complications may also include seizures and allergic reactions. Facilities providing pediatric sedation should monitor for, and be prepared to treat, such complications.

Back-up Emergency Services

A protocol for access to back-up emergency services shall be clearly identified, with an outline of the procedures necessary for immediate use. For non-hospital facilities, a protocol for ready access to ambulance service and immediate activation of the emergency medical services (EMS) life-threatening complications must be established and maintained. It should be understood that the availability of EMS does not replace the practitioner’s responsibility to provide initial rescue in managing life-threatening complications.

On-Site Monitoring and Rescue Equipment

An emergency cart or kit must be immediately accessible. This cart or kit must contain equipment to provide the necessary age- and size-appropriate drugs and equipment to resuscitate a non-breathing and unconscious child. The contents of the kit must allow for the provision of continuous life support while the patient is being transported to a medical facility or to another area within a medical facility. All equipment and drugs must be checked and maintained on a scheduled basis. Monitoring devices such as pulse oximeters, and defibrillators must have a safety and function check on a regular basis as required by local regulations.

Personnel

The Practitioner

The practitioner responsible for the treatment of the patient and/or the administration of drugs for sedation must be competent to use such techniques, to provide the level of monitoring required, and to manage complications of these techniques (i.e., to be able to rescue the patient). Because the level of intended sedation may be exceed, the practitioner must be sufficiently skilled to provide rescue should the child progress to a level of deep sedation. The practitioner must be trained in, and capable of providing, at the minimum, bag-valve-mask ventilation to be able to oxygenate a child who develops airway obstruction or apnea. Training in maintenance of advanced pediatric airway skills is required; regular skills reinforcement is strongly encouraged.

Support Personnel

The use of moderate sedation shall include provision of a person, in addition to the practitioner, whose responsibility is to monitor appropriate physiologic parameters and to assist in any supportive or resuscitation measures, if required. This individual may also be responsible for assisting with interruptible patient-related tasks of short duration. This individual must be trained in and capable of providing pediatric basic life support. The support person shall have specific assignments in the event of an emergency and current knowledge of the emergency cart inventory. The practitioner and all ancillary personnel should participate in periodic reviews and practice drills of the facility’s emergency protocol to ensure proper function of the equipment and coordination of staff roles in such emergencies.

SUMMARY

It is generally agreed that most fearful and uncooperative children can and should be managed with behavioral (nonpharmacologic) management techniques such as tell show do, positive reinforcement, distraction, modeling etc. Unfortunately, there are a
small percentage of pediatric patients that cannot be successfully managed solely through behavioral management techniques. When behavioral management strategies fail, some form of pharmacologic sedation or anesthesia becomes a valuable and necessary alternative. Various sedative agents and combination of these agents have been used to reduce anxiety and fear associated with dental treatment, producing variable results in terms of efficacy and safety. Midazolam, one of the commonly used oral sedation agent in children has several characteristics such as safety of use, rapid onset and some degree of amnesia that make it a desirable sedation agent in children. On the other hand, rather short working time allowed by midazolam sedation can be a limiting factor depending on the child’s dental treatment needs. Therefore, oral midazolam sedation is recommended for short dental procedures in children. It is emphasized again that Sedation Guidelines provided by the national and international professional bodies must be followed. The sedation provider and support staff must have appropriate training and place must be amply equipped before any sort of sedation is utilized for dental treatment of patients (of any age). A rescue system has to be in place if moderate sedation is planned, in addition to a mechanism of immediate transportation to a medical emergency room.

REFERENCES

Use of Oral Midazolam Sedation in Pediatric Dentistry: A Review


