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Midazolam: A Review of Its Pharmacological Properties and Its Therapeutic Use In Paediatric Patients

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Abstract

Behaviour management in uncooperative, highly anxious, or medically disabled child is a challenging process. In past, various drugs have been introduced in paediatric to facilitate treatment for particularly this group of patient. Midazolam is one such alternative drug which can be used as pharmacological behaviour management techniques during dental treatment procedure in paediatric patients. It is safe, effective and easy to administer for treating uncooperative child. However, further research on use of midazolam is needed in paediatric patients.

Keywords: Benzodiazepines, Conscious Sedation, Midazolam.

Introduction

Anxiety and pain in a child undergoing dental procedures is one of the major issue for a paediatric dentists. The majority of child patients can be managed by using non pharmacological behaviour management technique. Nevertheless, still many of them require pharmacological behaviour management technique. Since past many **sedatives** have been introduced in order to overcome this problem, for which Benzodiazepines are commonly used for treating such patients. Midazolam is a benzodiazepine which is available since 1983. It has a fast and short duration of action along with that it exerts an anxiolytic, anticonvulsive, muscular relaxant, and amnesic effects

[1]. They can be administered by various routes such as oral, transmucosal, intravenous, intramuscular, and rectal. In the present review the advantageous role of midazolam in the management of uncooperative child patients will be discussed [2].

Discussion

Midazolam: Class, Pharmacokinetics and Pharmacodynamics

Benzodiazepine has their main effect on specific receptors which are present in the neurons of brain. All benzodiazepine molecules have a common core shape, which could binds to these receptors. Normal passage of information from the peripheral senses to the brain is filtered by gamma- amino butyric acid system [2]. GABA it is an inhibitory neurotransmitter which emits from the sensory nerve endings as a result of stimuli [2]. This neurotransmitter is then binds to the receptors which is present on the cell membrane of the post-synaptic neuron and stabilizes it by increasing the threshold for firing. As a result, the number of sensory messages received by the brain is reduced when midazolam is given. When administered, it prolongs the effect of GABA which in turn reduces the number of stimuli reaching higher cortical center of brain which results in sedation, muscle relaxation, anxiolysis, amnesia, and anticonvulsant effects [2, 3]. Benzodiazepines need to cross the blood-brain barrier in order to reach their specific receptors site in brain. Midazolam can reach the brain very easily and quickly due to its lipophilic property [4]. Also, it is water-soluble, non-irritant, having a half-life of 6-15 minutes and an elimination half-life of 1.5-2 hours [4]. Therefore, it could be a safe and effective medicament in children because its elimination half-life makes it suitable for short-lasting duration procedures [5-8].

Uses of Midazolam

Midazolam in paediatric patient is used for two main purposes; conscious sedation, and premedication [4,9]. It can also be used to control seizure attacks [9]. In general, the use of midazolam is usually indicated in children who cannot cope up with treatment due to high levels of anxiety, uncooperative, young age child patients, learning difficulties, and/or an underlying medical condition. However, it is contraindicated in child patient with hypersensitivity to benzodiazepines, acute or chronic pulmonary disease, cardiac insufficiency, and myasthenia gravis [9]. Especially in young children, a serious disadvantage of using midazolam for conscious sedation is paradoxical reactions, that includes disinhibition, hallucinations, inconsolable crying, restlessness, agitation and disorientation [4,9,10]. Certain drugs may interact with midazolam, which include erythromycin and clarithromycin, fluconazole and ketoconazole, and some antivirals like such as efavirenz, fosamprenavir, and nelfinavi. These drugs results in increasing or prolonging plasma concentration of drug [2,7,10]. Midazolam can also enhance the hypotensive effect of calcium channel blocker [9, 11]. These effects should be taken into consideration before giving midazolam to a child patient. Another side effect of using midazolam is respiratory depression. Therefore, it is vital that oxygen along with all required equipment for the management of respiratory depression should be available [9]. Decrease in mean arterial pressure, cardiac output systemic vascular resistance, and stroke volume has also been reported just immediately after drug administration [3]. Flumazenil is the reversing drug used in order to treat reverse over-sedation, respiratory depression, and/or paradoxical reactions caused by benzodiazepines. No paediatric dose has been recommended by the manufacturer and nor it is licensed for use in children. The adult dose is 0.2 mg

intravenously, given administered over 15 sec. Proportional dosage reduction of dosage in children has been recommended by taking into consideration with the dose of IV flumazenil as 0.01 mg/kg [9)]. It is worth mentioning noteworthy that the half-life of flumazenil is shorter than that of midazolam, therefore, sedation may occur recur when the patient has reached home [3].

Conscious sedation

It is defined as a minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command and that is produced by a pharmacological or non pharmacological method or a combination thereof [12].During conscious sedation, no interventions are required to maintain a patent airway, spontaneous ventilation, and cardiovascular function is usually maintained [13, 14]. The drugs and techniques used to provide conscious sedation for dental treatment should carry a margin of safety sufficiently wide enough to render loss of consciousness unlikely [15]. Conscious sedation is used as an adjunct to the behaviour management techniques for treating child patients in the dental setting as it avoids major risks associated with general anaesthesia and aims for behaviour improvement, and anxiety reduction [1]. In a Cochrane systematic review the authors were not able to draw a conclusion regarding the most effective drug or method of sedation for anxious children [16]. However, midazolam use for conscious sedation is a most appropriate option in paediatric dentistry. Patient selection should be specific for conscious sedation with midazolam. American Society of Anesthesiologists (ASA) considers Class I or Class II patients to be the candidates for conscious sedation. [12, 13]. As mentioned earlier, there are various routes of administration of midazolam which can be use for conscious sedation. The oral route of administration is the most widely used in children as it is easy to administer and there are decrease chances of risks for of allergic reaction. However, when taken orally, the onset and duration of action of midazolam is prolonged, and a stable sedative level is attained within 30 minutes after drug intake [17-19]. A higher oral dosage of drug (0.3-0.5 mg/kg up to 12 mg maximum) is required because bioavailability of midazolam is decreased when it passes to the portal circulation to reach systemic circulation [9].The oral route is useful in needle phobic children and medically compromised children who cannot cope with dental treatment. However, the oral intake is completely dependent on the compliance of the child patient [9]. Also, there is no liquid form of drug is available. Therefore, the IV solution is mixed with a suitable juice in order to reduce the strong, bitter taste. For optimal sedation, the drug should be administered 10-20 minutes prior to procedure. One research has shown that when midazolam is mixed with Pepsi cola (PepsiCo, Harrison, NY, USA), 10% sodium citrate, pomegranate juice, and grapefruit juice for oral intake the drug ingestion was simpler and conscious sedation was more effective as mixture contains sodium citrate which helps in reducing the gastric pH, which further results in better absorption of the drug [20]. Another study showed that the use of oral intake for sedation was well tolerated by children [21]. Wilson *et al.* [22] investigate the effectiveness of 0.5 mg/kg oral midazolam sedation for orthodontic extraction. They concluded that oral sedation using midazolam was safe and acceptable by 10-16 years of age old patients. In another study, oral sedation found to be safe and effective as compared to nitrous oxide sedation but it was not the method of choice for all patients [23]. This reason could be the unpleasant taste of the oral solution or the paradoxical reactions. Transmucosal, intranasal route of

administration is another alternative method in child patients for sedation. The sedative effect is observed within 5 min of administration by administering 0.1-0.2 mg/kg midazolam intranasally or transmucosally. Studies have also shown the rapid onset of action (5-10 minutes), as well as the short recovery time following administration of intranasal midazolam sedation [24]. Compared to oral administration, intranasal midazolam is absorbed rapidly from the nasal mucosa with instant peak effects of the drug. Therefore, the nasal route could be a better option in young children. Another disadvantage is that if large volumes of the solution is administered it can cause coughing, sneezing, and expulsion of the drug [9]. Also when used intranasal midazolam can result in nasal irritation along with nasal discharge [25] and could lead to occasional respiratory depression [26] Karl *et al.* [27] compared intranasal and sublingual routes of administration of midazolam. Their results revealed that sublingual route of administration was as effective as intranasal route and also well accepted by paediatric patients. The Intravenous (IV) route is another most common route of drug administration of midazolam. The advantage of using this route include rapid onset (3-4 minutes) with adequate patient cooperation, ability to titrate the dose, and good amnesia [28)]. The recommended dose for Intravenously in children is 0.25-1.5 μg/kg/min. The drug must be administer slowly so that its side effects are assessed and overdosage is avoided [4]. Robb *et al.* [28] reported cases of conscious sedation with IV midazolam in 11-15 years old children. No loss of consciousness or fall in oxygen saturation levels was observed, which indicates that this drug is safe for conscious sedation. While sedating a child by using any of the above- mentioned routes all vital signs should be monitored, especially when midazolam is administered by the oral or IV route [2, 24, 29, 30]. Using pulse oximeter throughout conscious sedation is mandatory in order to take action if any unnecessary complication occurs.

Premedication for induction of general anaesthesia (GA) induction

Induction of General could be challenging in a highly anxious patient, and medically compromise patient. Various medications have been introduced in order to ease child-separation anxiety from the parents. The ideal premedication should have an acceptable route of administration, should have a rapid onset of action and rapid elimination [31]. It has been reported that midazolam fulfils these mentioned criteria and, therefore, it can be used as a premedication agent before dental treatment under general anaesthesia GA [6, 32, 33]. Wilton *et al.* [34] was the first to describe the use of intranasal midazolam conscious sedation as premedication. Weber *et al* [35] in their study showed that the intranasal route of administration for midazolam was an appropriate premedication in preschool children.

A placebo-controlled trial reported the reaction time and psycho-motor coordination of children undergoing general anaesthetic before discharge and at 48 hours when premeditated with 0.2 mg/kg buccal mucosa injection of midazolam to a maximum dose of 10 mg was assessed. Results revealed that reaction time was significantly slower and the psycho-motor coordination was also significantly impaired in the midazolam group. Midazolam was also associated with anterograde amnesia [36]. This indicates that impairment of children's cognitive function lasts for up to 48 hours post-GA should be expected when midazolam is used as a premedication. Also in a study, the authors showed that if 0.2 mg/kg buccal midazolam reduced anxiety in most patients [37]. Kain *et al.* [38] said that children when premedicated with oral midazolam showed exhibited less negative behavioural changes during the first postoperative week

visit when compared to those in the placebo group. It has been suggested that high levels of trait anxiety could be a contraindication to the use of oral midazolam as a premedication for general anaesthesia GA [39]. Regarding recovery and discharge times, Viitanen et al. [40] showed that the use of oral midazolam as premedication for propofol - induced GA in 1-3 year old children delayed early recovery but did not affect discharge time. The authors also concluded that oral midazolam did not improve the quality of recovery. Last but not the least, midazolam could be used as an emergency drug in the dental set up.

Conclusion

A child visit to paedodontist is concerned with a major challenge. Fear and anxiety could lead to avoidance of treatment. Child dental anxiety is widely acknowledged as the main source of behavioural problem in the dental office. These cases are well treated by pharmacological management using sedative agents. Midazolam is one such pharmacological behaviour management which can be used to reduce anxiety in young children. Midazolam, like any other drugs has its own side effects which that could lead to complications like respiratory depression. Therefore, practitioners should be skilled enough to manage such complications in case of an unforeseen circumstances. In the dental set up where midazolam sedation is used, the midazolam reversal drug, that is flumazenil, should always be kept in order to avoid complications.

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