A Panorama of the Applications of Midazolam in Dentistry and Recent Advances

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ABSTRACT

The prevalence of dental fear is ubiquitous and so is the need; to remove fear and anxiety. Depression of the individual’s consciousness during the treatment aids tremendously in a positive patient outcome. It also contributes to a better overall oral health of the community. All the sedative agents of old have either caused more harm than good or failed in their effectiveness. With the introduction of midazolam in 1975 sedation has not only become safe but also highly effective. Midazolam acts by enhancing the activity of the GABA receptors in the central nervous system. Alongside the sedative effect, the drug shows anxiolytic, muscle relaxant, anticonvulsant, hypnotic and amnesic properties. Literature supports the use of midazolam as an emergency drug for seizures, for conscious sedation and as a part of the pre-anesthetic medication. Midazolam has been used extensively to achieve positive behaviour in children undergoing dental therapy. Certain side effects have been reported with the use of this drug. With modern delivery systems such as Mucosal Atomization Device (MAD), the rapidity of onset of the drug is enhanced along with a reduction of the dose. This review article stands as a testimony to the use of midazolam in dentistry.

Key Words: Dental Fear, Anxiety, Midazolam, Sedation Dentistry, Conscious Sedation, Mucosal Atomization Device

INTRODUCTION

Fear is an unpleasant feeling often caused due to the awareness of danger or hurt.¹ The most pragmatic way to define fear is as the neurophysiological processes that prepare an organism to perform innate or learned responses to cope with danger.²³ Dental fear has been a significant contributor to the evasion of dental health care.⁴⁻⁵⁻⁶

Anxiety precedes fear, wherein anxiety occurs before the presence of a stimulus that, more often than not, is threatening.⁷ Anxiety alters reality which leads to patients experiencing a change in the quality of pain perceived by them and instils an everlasting pain-tinted dental experience.⁷ the dentist has to identify the aspects of the dental setting which would likely aggravate the anxiety, the need for the current appointment and the previous dental experiences of the patient.⁷⁻¹⁰⁻¹¹ The components of pharmacological anxiolysis include sedation and general anaesthesia.¹² Factors to be considered are the risks of the pharmacological management versus benefit, selection of the appropriate drug, the level of anxiety, dentist’s expertise, presence of equipment and emergency care.¹³

Sedation is defined as the use of a drug or combination of drugs to depress the central nervous system, thus reducing patients’ awareness of their surroundings.¹⁴ Conscious sedation has been employed as a means to remove fear and anxiety from dental care and it is considered of paramount importance. Anxiolysis is a drug-induced state during which patients respond normally to verbal commands.¹⁵⁻¹⁶ It is mandatory to note that the use of conscious sedation should be taken bearing the patient’s thorough medical and dental history. Barbiturates were a few of the earliest sedative agents used for conscious sedation. With the introduction of benzodiazepines (Midazolam), conscious sedation included anxiolysis along with profound amnesia. They are considered the gold standard in sedation and are regarded as very safe drugs.¹⁷

The dentist must alleviate the anxiety and fear as it can cause exhaustion post-treatment and a ripple in the normal facets of one’s daily activities including personal, social interactions...
Midazolam as a sedative has made a significant contribution towards conscious sedation. A plethora of studies backs midazolam in terms of efficiency, ease of administration and safety. This article provides a meticulously prepared agglomerate of the scientific literature with regards to the use of midazolam for conscious sedation in dental practice.

HISTORY

The need for the removal of fear and pain from the dental office has existed as long as the existence of the art of dentistry. In the 15th century ether was used as the first anaesthetic agent alongside, a distillate of sulphuric acid and diethyl ether called ‘sweet oil of vitriol’ which was widely used in dentistry. The 17th century saw the discovery of nitrous oxide by Joseph Priestley. Humphrey Davy commented on the uses of nitrous oxide in surgeries and its potency in alleviating pain. The first benzodiazepines were created by Hoffmann-La Roche and Leo Sternbach in 1955. Diazepam (Valium) was discovered a little later but grew very famous. Molecular changes were made to meet the demands and also counteract any undesirable quality. Midazolam was created in 1975 by Walser and Fryer.

CHEMICAL STRUCTURE

Midazolam is a water soluble, crystalline yellow to white salt. The IUPAC name for midazolam hydrochloride is 8-chloro-6-[(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine hydrochloride and the molecular formula is C18H11ClFN3.HCl. In low pH the salt is hydrophilic and has an open diazepine ring which closes shut at high pH to form the physiologically active lipophilic product as in Figure 1. It has a molecular weight of 325.8 g/mol.

MECHANISM OF ACTION

Midazolam is a short-acting benzodiazepine with pharmacological uses such as anxiolytic, amnestic, muscle relaxant and sedative uses. The mechanism of action of midazolam as a sedative is based on its effect on the GABA (gamma-aminobutyric acid) receptors. It works by enhancing the affinity of the GABA to the GABA receptor. GABA is a major inhibitory neurotransmitter present in the central nervous system. Benzodiazepines do not have a direct agonistic activity on GABA rather it has a boosting effect on the action of GABA. The GABA receptors are classified into GABA1 and GABA2 receptors. GABA1 receptors have subtypes α1 and α2. Of these α1 subtype mediates sedation, anti-convulsant and amnesia activity while the α2 subtype mediates anxiolysis and muscle relaxation. They do not act on GABA receptors.

Midazolam has both hydrophilic and lipophilic properties depending on the pH of the solution. When midazolam is absorbed it has to bio transform through both the microsomal oxidation and glucuronide conjugation. First, it gets hydroxylated with the help of cytochrome CYP3A4, CYP3A5. Through the hydroxylation process two pharmacologically active agents namely, α-hydroxymidazolam and 4-hydroxymidazolam are formed. They undergo rapid glucuronide conjugations to form pharmacologically inactive compounds. Midazolam gets bounded to the plasma protein and is well distributed.

PHARMACOKINETICS

Absorption

Midazolam is available in its salt form which is hydrophilic and maintains its hydrophilicity at a low pH. The oral midazolam tablet often stays hydrophilic due to the low pH in the stomach. With the change in pH in the gastrointestinal tract to the physiological pH, the ring structure of midazolam closes forming the lipophilic form. Midazolam is absorbed through the gastrointestinal tract following oral administration, with peak effect 30-90 minutes after administration. Owing to the first pass metabolism only 40-50% of the administered dose reaches circulation. Midazolam has shown rapid onset and increased bioavailability of 90% through the intramuscular route. The intranasal route of administration has shown superiority in the onset duration and ease of use when compared with the oral route. It is important to consider the painless quality of the intranasal route compared to the intramuscular and the intravenous routes.

Distribution

Midazolam distribution is higher among obese people as it gets distributed to the adipose tissue. The volume of distribution has been found to be 1-2.5 l/kg. The distribution is
greater in women compared to men. Midazolam has a good affinity to plasma proteins and is mostly bound to them only about 4% of the given dosage is available as free faction.

Elimination
Metabolites of midazolam in the form of α-hydroxymidazolam and glucuronide conjugate are excreted by the kidney through urine. Almost all of the midazolam gets conjugated, less than 0.5% gets excreted unchanged. The plasma clearance seemed to increase in patients in supine position owing to the 40-60% increase in the hepatic blood flow.

PHARMACODYNAMICS
The action of midazolam in the body is chiefly based on its highly sedative potency. Besides its sedative nature, it has antiepileptic properties, acts as a muscle relaxant and causes anterograde amnesia. Once the effect wears off, the patient’s cognitive and psychomotor skills are retained. Minimal cardiovascular changes are evoked by this drug. Midazolam could decrease vascular resistance. Midazolam causes an increase in the frequency of respiratory rate with a decrease in tidal volume. It leaves the cortisol and renin responses unaltered during surgical stress. It preserves the blood flow to the brain and myocardium while reducing flow to the liver and kidneys.

SIDE EFFECTS
Midazolam like any other drug is a slave to the side effects it manifests. The side effects are cardiac arrest, heart rate variations, a fall in blood pressure, convulsions, anaphylaxis, thrombosis, laryngospasm, bronchospasm, respiratory depression, gastrointestinal changes, xerostomia, hiccup, increased appetite, jaundice, drowsiness, confusion, dysarthria, urinary retention or incontinence, blood disorders, muscle weakness, visual disturbances including diplopia, salivation changes, skin reactions along with any skin changes in the intravenous route injection site. When given through the intranasal route, midazolam is known to produce a burning sensation, irritation to the nasal mucosa and lacrimation. When taken orally there is a delay in onset and there is no IV access for a reversal agent in case of overdose.

DRUG INTERACTION
Drug interactions between midazolam and other drugs are chiefly governed by the cytochrome P450 oxidase system in the liver where midazolam gets metabolized. Drugs such as cimetidine, ranitidine, omeprazole, macrolides and oral contraceptives inhibit the metabolism of midazolam causing reduced clearance and increased half-life. Rifampin is a cytochrome P450 enzyme inducer that increases the clearance of midazolam.

DISCUSSION
Midazolam has shown anxiolytic, sedative, muscle relaxant, anticonvulsant, hypnotic and amnesic properties which can be exploited in the dental setting.

Midazolam as an emergency drug in the dental office
Seizures are commonly encountered in the dental office with a worldwide prevalence of 0.5-0.9%. The management of epilepsy is achieved through the depression of the central nervous system which could be achieved with benzodiazepines. Midazolam has been included in the additional emergency drugs for the management of dental emergencies. The muscle relaxant property of midazolam has been exploited in the rapid sequence intubation for establishing a patent airway in the emergency department in dosage of 0.1mg/kg. Besides these the property of amnesia, anxiolysis and sedation play their role in making midazolam a must-possess emergency drug.

Midazolam as a pre-anaesthetic agent in the pediatric population
Children in the initial stage of anaesthesia could experience unpleasantness, have anxiety and suffer from separation from parents leading to hypersalivation, breath-holding and laryngospasm. Besides these, there could be traumatic experiences deeply rooted in the child’s mind from the induction room. Midazolam is chosen as a pre-anaesthetic medication as it is predictable and has good patient acceptance. It is consistent and has few side effects which are the ideal characteristics of a premedicament. Various drug dosages have been tried by various authors when using midazolam as a pre-anaesthetic agent. The most effective dosage and safest dose for children has been identified as 0.75mg/kg considering the age of the child.

Midazolam in conscious sedation
Conscious sedation in dentistry plays a major role in achieving a positive psychological effect on the patient while also preserving the consciousness and the responsiveness to verbal commands. Midazolam is one of the most commonly used benzodiazepine drugs. In conscious sedation, the consciousness of the patient remains uncompromised as compared to general anaesthesia and deep sedation; hence it provides a wide margin of safety.
The intranasal route has the benefits such as a large surface area of the nasal mucosa and the drug escapes the first-pass metabolism. Though various anatomic, physiologic and drug characteristics play a major role in the absorption one of the most important criteria is that the drug needs to be lipophilic for absorption to occur through the mucosa. Literature claims the intranasal route to be effective in terms of ease of use and reduced duration of onset with a dosage of 0.3-0.5mg/kg.

Studies indicate intravenous midazolam given at 0.06mg/kg dosage produced adequate anxiolysis. The onset was significantly faster. 5 minutes post-administration the effects of sedation started to manifest. The children administered IV midazolam showed lesser movement in-between treatments, cried less and mostly fell asleep during the entire procedure. The intranasal route has the benefits such as a large surface area of the nasal mucosa and the drug escapes the first-pass metabolism. Though various anatomic, physiologic and drug characteristics play a major role in the absorption one of the most important criteria is that the drug needs to be lipophilic for absorption to occur through the mucosa. Literature claims the intranasal route to be effective in terms of ease of use and reduced duration of onset with a dosage of 0.3-0.5mg/kg.

CONCLUSION

Of the many challenges that confront the dentist, the obliteration of fear from the dental setting proves fit to test the mettle of the dentist. Midazolam has made sedation easy for patients and dentists alike. Midazolam is very safe for use in the pediatric population, where the need to remove fear is even more important to develop a positive attitude in children, which would drastically improve their overall oral health. With the introduction of newer technologies, the figments of painless, fearless dentistry have come closer to reality.

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Author’s Contribution

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