

Sedation with oral benzodiazepines in dental practice in cardiac patients: a literature review

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ABSTRACT | There are different types of sedation used for performing medical and dental procedures. The medications most commonly used for this purpose are benzodiazepines, which are considered safe and effective in the hospital or outpatient dental practice. However, in dental clinical practice, they are underutilized, especially in patients with cardiovascular disease. The aim of this study was to address the use of benzodiazepines as oral sedatives, their indications, contraindications, and peculiarities, as well as their correlation with cardiac patients, through a literature review. Sedation or minimum anxiolysis is a drug-induced state during which patients respond normally to verbal commands and airway reflexes, while respiratory and cardiovascular functions are unaffected. The beneficial effects of benzodiazepines include reduced anxiety, sleep induction and maintenance, muscle relaxation, and treatment and prevention of epileptic seizures. Benzodiazepines are indicated for patients with anxiety but should be used with caution in patients with serious illnesses, pregnancy or using other central nervous system depressants. Its use in cardiac patients is safe and effective because it reduces the hemodynamic function. It is important for the dentist to know and use this class of medications, improving the quality of care for the cardiac patient.

KEYWORDS | Benzodiazepines; Heart Disease; Dentistry.

RESUMO | **Sedação com benzodiazepínicos orais na prática odontológica em pacientes cardíacos: uma revisão de literatura** • Existem diferentes tipos de sedação utilizados para a realização de procedimentos médicos e odontológicos. As medicações mais comumente usadas para este fim são os benzodiazepínicos, considerados seguros e efetivos na prática odontológica hospitalar ou ambulatorial. No entanto, na prática clínica odontológica, eles são subutilizados, especialmente em pacientes com doenças cardiovasculares. O objetivo deste estudo foi abordar o uso de benzodiazepínicos como sedativos orais, suas indicações, contraindicações e peculiaridades, bem como sua correlação com pacientes cardíacos, através de uma revisão da literatura. Sedação, ou ansiólise mínima, é um estado induzido por medicamentos, durante o qual os pacientes respondem normalmente a comandos verbais e reflexos das vias aéreas, enquanto a função respiratória e cardiovascular não é afetada. Os efeitos benéficos de benzodiazepínicos incluem redução da ansiedade, indução e manutenção do sono, relaxamento muscular e tratamento e prevenção de convulsões epiléticas. Benzodiazepínicos são indicados para pacientes com ansiedade, mas devem ser usados com cautela em pacientes com doenças graves, gravidez ou que utilizem outros depressores do sistema nervoso central. É importante que o dentista conheça e use esta classe de medicamentos, melhorando a qualidade de atendimento para o paciente cardíaco.

PALAVRAS-CHAVE | Benzodiazepínicos; Doença Cardíaca; Odontologia.

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INTRODUCTION

There are different types of sedation used for conducting medical and dental procedures. Each type of sedation will lead to a patient's response, who must be aware of the entire process, and, to be performed, it requires professionals with specific techniques and skills. The type of sedation should be appropriate for each patient and each procedure to be performed.¹

It is already well established in literature that anxiety, discomfort and pain can be reduced during dental procedures, and the use of conscious sedation requires dosages that allow verbal communication during procedures. The most commonly used medications for this purpose are benzodiazepines, considered safe and effective in the hospital or outpatient dental practice.^{2,3}

It is important to note that surgical procedures involving a high level of emotional stress release endogenous catecholamines in response to neurohumoral stimulation and, when combined with the use of local anaesthetics with a sympathomimetic vasoconstrictor, might cause changes in the cardiovascular system. This poses risks that can be greater than those expected in conscious sedation, especially for those with systemic diseases.⁴

However, few dentists use these drugs in clinical practice, perhaps for lack of knowledge on the benefits of these medicines or by uncertainty regarding the side effects of the treatment, especially in patients with cardiovascular disease.

Therefore, the aim of this study was to address the use of benzodiazepines as oral sedatives, their indications, contraindications, and peculiarities, as well as their correlations with cardiac patients.

MATERIALS AND METHODS

This literature review was conducted in the PubMed database, regardless of the year, using the following descriptors: (benzodiazepine oral) OR (oral sedative premedication AND cardiac patients) OR

(oral benzodiazepines AND cardiology) OR (oral benzodiazepines AND heart disease).

LITERATURE REVIEW

Benzodiazepines

According to the Academy of Medical Royal Colleges, there are several levels of sedation. Sedation is an individual state of depression of consciousness, with dose-response dependent on the drugs used, which can result in loss of consciousness. In light sedation, or anxiolysis, verbal responses are maintained; there is no change in the airway, breathing and cardiovascular function. In moderate sedation, commonly known as conscious sedation, there is a response to verbal and tactile stimulation, respiratory assistance and adequate ventilation are not required, cardiovascular function is generally maintained, and it is considered safe. In deep sedation, there is no response to stimuli, it is necessary to intervene in breathing and ventilation, while cardiovascular function is usually maintained.⁵

The American Society of Anesthesiologists defines minimal sedation, or anxiolysis, as “a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected.”⁶

Surgical procedures can lead to a high level of anxiety, especially in children, which may cause significant medical, psychological and social consequences. One way to alleviate this suffering preoperatively may be administering sedatives that will thus facilitate the time of anesthesia. The effects of sedative medications might be: amnesia, anxiolysis, decreased psychological stress and reduced need for general anesthesia.^{7,8}

In the late 1970s, benzodiazepines have become commonly prescribed drugs worldwide. Due to their sedative effect combined with low toxicity, they were

considered the ideal conditions for many common medicines.⁹

In Brazil, stress and pain control in dental practice is not routine, probably due to the lack of attention given to this issue during the training of the dentist, even regarding the most known forms of sedation, such as the oral use of benzodiazepines. Anxiety concerning dental treatment is still very common, a factor that often prevents adherence to the treatment.^{10,11}

Sedative medication has great benefits in children, adolescents, patients with negative past history associated with hospitalization and patients with limited cooperation and communication.⁷

According to Baldwin et al. (2013), the beneficial effects of benzodiazepines include reduced anxiety, induction and maintenance of sleep, muscle relaxation, and treatment and prevention of epileptic seizures. These are properties of various benzodiazepines in different degrees, which will depend on their potency, pharmacokinetic properties and their connection with the receptors of the gamma-aminobutyric acid (GABA).¹²

Benzodiazepines specifically activate the inhibitory neurotransmitter GABA_A receptor chloride, increasing GABA activity and neuronal depression by reducing the metabolism and cerebral blood flow.¹³

According to scientific literature, respiratory depression is an adverse effect of benzodiazepines and, therefore, caution should be taken if the patient has chronic respiratory failure.¹⁴

They should also be used with caution in patients who are treated with other central nervous system depressants, patients with kidney or liver disease, severe congestive heart failure, in pregnancy and during lactation.¹⁰ In these cases, in order to perform sedation safely, some parameters must be followed:¹⁵

- Perform previous assessments and associated comorbidities;
- Assure that the patient is fasting;

- Assess the duration of the procedure;
- Knowledge on the importance of pharmacology of drugs used and antagonists;
- Conduct monitoring and recovery of the patient;
- Have onsite support necessary for emergency airway rescue manouvres, if necessary.

Among the unwanted effects of benzodiazepines are delirium, disorientation, hallucinations, disinhibition, aggression, tolerance, and dependency, if used continually and indiscriminately. The paradoxical effects are more common in children and in the elderly, with low incidence when used in a single dose.^{2,9,10,12}

Small doses of benzodiazepine anxiolytics have a little clinically significant effect on cardiorespiratory function, but high parenteral dosage may cause loss of upper airway muscle tonus, decreased ventilatory response, and decreased systemic vascular resistance, thus requiring a higher level of monitoring.¹³

Furthermore, one of the great advantages of using conscious sedation is the reduced anxiety and patient discomfort, which decreases the risks that might be caused by general anaesthesia.¹⁶

Another great advantage is the presence of a benzodiazepine antagonist drug that reverses the sedative, hypnotic, and respiratory suppressive effects, flumazenil. Flumazenil is an imidazobenzodiazepine that competitively antagonizes the same receptor; it can be used intravenously or intranasally. Reversal effects are noticeable within 1-2 min and peak in 6-10 min. The duration of flumazenil's effect is 30-60 min, with an elimination half-life shorter than Midazolam.²

Diazepam

Diazepam is a long-acting benzodiazepine often used for sedation, amnesia induction, or pre-procedure. It is rapidly absorbed after oral

administration. Despite a long half-life of 30 to 60 hours, the clinical term sedation after oral administration is much shorter than expected, due to its rapidly changing distribution outside the central nervous system. The elimination half-life and systemic availability of benzodiazepines also vary significantly with the age, sex, and weight of the patient.¹⁷

Its onset of action occurs in about 60 minutes; however, it is not used for short dental procedures because its effect can last 12-24 hours. The usual dosage is 5-10mg for adults, 5mg for older people, and 0.2-0.5mg / kg for children.¹⁰

Although pharmacokinetic studies suggest that Midazolam would be preferable than Diazepam, in a randomized sedation for cardioversion comparing Diazepam and Midazolam, the effectiveness of sedation and amnesia was the same, but the normalization of the mental test score was much faster with Diazepam. This early wakefulness may have advantages for monitoring recovering patients after the procedure.¹ Both drugs are in the list of essential medicines recommended for the health of the majority of the population.¹⁸

In a study by Ashraf et al. (2015), in a sample of 93 elderly and cardiac patients who would undergo a catheterization procedure, 47 patients were orally premedicated with diphenhydramine 25 mg and Diazepam 5 mg, while the others did not receive medication. The author noted that none of the patients in both groups developed delirium. The cooperation of the patient, the ease of the procedure and reduced need for medication before and during the procedure were higher in pre-medicated group.¹⁹

Midazolam

Midazolam has a faster onset of action following oral administration of approximately 30 minutes, and a short duration of action with an elimination half-life of approximately 2 hours (1-4 hours). This pharmacokinetic profile makes oral Midazolam

an adequate preoperative medication for minor surgeries.^{10,20} It also has a known anterograde amnesic effect.²¹ Due to these properties, it is the most commonly used sedating medication in children.⁷

Midazolam can be administered intravenously, intramuscularly, intranasally, rectally and orally with varying doses and respective action.² The usual dose for adults is 7.5-15 mg, 7.5 mg for the elderly and 0.25-0.5 mg/kg for children.¹⁰

Abdul-Latif et al. (2001) conducted a placebo-controlled, randomized, double-blind prospective study to evaluate the pre-anaesthetic efficacy of oral Midazolam 7.5 mg in 50 ASA I and II patients scheduled for breast surgery. The results of the study indicated a small decrease in heart rate and systolic blood pressure, and the induction of general anesthesia was obtained with a lower dose of propofol.²⁰

In a comparative, prospective, randomized, and double-blind study performed by Middlehurst et al. (1999), 50 ASA III and IV cardiac patients with dental problems were divided into two groups. Group 1 used anaesthesia with 2% lidocaine, epinephrine 1: 50,000 and vasopressin 0,25UI / ml for performing dental procedures, while Group 2 used the same anaesthesia associated with sedation with intravenous Midazolam. There was no difference between groups. The authors stress that Midazolam should be given as a protocol in performing dental procedures in cardiac patients.²²

Shibuya et al. (2003) conducted a retrospective study of 25 patients with hypertrophic and dilated cardiomyopathy, in which the heart function was assessed by echocardiography and electrocardiography during the dental procedure. The patients were divided into 3 distinct groups. In the first group, invasive procedures were performed under local anaesthesia; in the second group, non-invasive procedures were conducted under local anaesthesia; and in the third one, non-invasive

procedures were performed without anaesthesia. Sedation was performed with Midazolam, Diazepam and Flunitrazepam in intravenous doses. A total of 87 dental treatment sessions were held, and it was observed that 40% of patients reported dental fear. The authors found no relation between the types of anaesthetic, and sedation did not influence the cardiovascular alterations found on the electrocardiogram.²³

The control and prevention of adverse effects of benzodiazepine agents on the central nervous and cardiovascular systems, such as anxiolytics, were reported by several authors, and Midazolam is the drug of choice since it has faster effects and shorter duration than other medications.⁴

Studer et al. (2012) evaluated the use of Clonidine 150 mg compared to Midazolam 7.5 mg for premedication in surgical extraction of the third molar. It was a prospective, randomized, crossover, double-blind study, in which 10 patients undergoing bilateral dental extraction received Clonidine or Midazolam orally 1 h before treatment. Patients who received Midazolam for the first surgery received Clonidine in the second operation and vice versa. There was no significant difference between both drugs, and patient satisfaction did not differ between groups.²⁴

Alprazolam

Alprazolam, when compared to other benzodiazepines, has the highest anxiolytic activity, with an onset of 1.4 hour and an elimination half-life of 10.6 hours. Its main effects are the reduction of anxiety and panic attacks in patients, thus being a possible alternative premedication for surgical patients.²⁵

Alprazolam is an anxiolytic agent used as pre-medication due to its short half-life, rapid effect and ease of use when compared to other benzodiazepines.²⁶

Its effect lasts for about 1-2 hours and it has a lower incidence of paradoxical effects or anterograde

amnesia, being a good alternative to sedation. Its usual dose is 0.5-0.75 mg for adults, 0.25-0.5 for the elderly, and, for children, Alprazolam is not indicated.¹⁰

As oral premedication, Alprazolam 0.5 mg decreased anxiety in the same proportion as Midazolam 0.75 mg. In 80% of patients, Alprazolam was as effective as Midazolam to reduce anxiety, but their amnesic effects were not.¹⁰

A study by Kim et al.²⁵ compared the use of pre-surgery sedation in 58 patients; Alprazolam 0.5 mg showed a lower incidence of amnesia in comparison with Triazolam 0.25 mg in the study sample. No cases of respiratory depression, emergencies or other effects were reported.

Cubuk et al. (2011) evaluated the heart rate variability during coronary angiography procedure and concluded that Alprazolam reduces anxiety, decreases heart rate variability and improves the quality of imaging.²⁶

Triazolam

Triazolam is premedication used for anxious patients or patients with severe insomnia. Despite its potential hypnotic, amnesic, anxiolytic, sedative, anticonvulsant and muscle relaxant effects, it is generally not indicated as a premedication by anesthesiologists because of its persistent effects. Compared with other benzodiazepines, Triazolam has a rapid onset and short duration of action. It is able to induce a state of drowsiness with minimal effects on respiration and myocardium. The peak effect is reached in approximately 1 hour, and its effects are sedation, amnesia and reduced anxiety.²⁵

Due to its potential to anterograde amnesia, the faster onset of action and a shorter plasma half-life, from 1.5 to 5.5 hours, Triazolam was chosen in a study by Fabian et al. (2006) as sedative administered orally prior cardioversion in patients with atrial fibrillation. Cardioversion is a method to restore normal sinus rhythm, but the disadvantage

is that the delivered cardioversion shocks are usually carried out without anaesthesia or sedation, causing a painful experience for patients. Previous use of Triazolam decreased anxiety, discomfort, pain and caused amnesia in some patients compared to placebo.²⁷

The usual doses used orally are 0.125-0.25 mg for adults, 0.06-0.125 mg for the elderly, and, for children, it is not recommended; this medication would be ideal for use in the elderly due to its rapid onset and short duration of action, but it is not commercially available in Brazil.¹⁰

Lorazepam

Lorazepam is the ideal drug for sedation of geriatric patients; its plasma half-life is an intermediate between Triazolam and Diazepam, and it has a lower incidence of paradoxical effects. The time required for the onset of drug effect is 1-2 hours, the plasma half-life is 12-20 hours and the duration of effects is 2-3 hours. In older adults, the usual dose is 1 mg, and 1-2 mg for adults; it is not suitable for children.¹⁰

Saccomarmo et al.²⁸ compared the effects of Lorazepam alone and Lorazepam, morphine, and perphenazine on cardiorespiratory variables, sedation, and anxiety in patients scheduled for coronary artery bypass graft. The authors concluded that Lorazepam alone can be used safely as a premedication in patients with critical coronary artery stenosis.

DISCUSSION

Medications such as anxiolytics are not widely used for minor surgery due to possible complications in the postoperative period, besides causing delayed recovery from anaesthesia and patient discharge.²⁰

However, oral benzodiazepines are an effective and safe alternative to control anxiety during dental treatment. The use of Benzodiazepines is indicated to reduce anxiety, induce and maintain

sleep, muscle relaxation, and to treat and prevent seizures. They are contraindicated for patients with chronic respiratory failure or who use other drugs or substances that cause central nervous system depression.^{3,7,12,14}

In scientific literature, there is a predominant use of Midazolam due to the effects of rapid onset and shorter duration than others; however, Diazepam has the same effectiveness in sedation. Alprazolam and Triazolam, in addition to their anxiolytic properties, have great potential for amnesia. Lorazepam is the medication of choice for the elderly due to lower prevalence of paradoxical effects. Flumazenil has a major advantage of benzodiazepines compared to other sedative drugs, with a rapid antagonistic effect on sedatives, easily reversing sedation.^{1,2,10,20,25}

Cardiovascular reactions are common in surgical situations and may be related to the response to the activation of α and β -adrenergic receptors, resulting in increased cardiac output, increased peripheral vascular resistance and a possible increase in blood pressure and heart rate, varying from individual to individual. This difference reflects the variability in the adrenal sympathetic activation, which leads to the release of epinephrine and norepinephrine during a stressful situation.⁴

Thus, oral sedatives such as benzodiazepines should be used to reduce anxiety, pain and discomfort of patients, improving the quality of care, its safeness and effectiveness. Although cognitive function and physical coordination may be impaired, this drug does not significantly affect airway reflexes and respiratory and cardiovascular functions if used rationally; so, it can be used safely in patients diagnosed with heart disease.^{3,7,8,13}

It is important that the professional conduct a thorough examination and be able to perform sedation and know the pharmacology of benzodiazepines. There should be an incentive for the use of these drugs by the dentist because of the benefits it shows.¹⁵

From this literature review, we conclude that:

1. Benzodiazepines are indicated as oral sedatives, but are underused in dentistry;
2. They are indicated for patients with anxiety when facing a stressful situation, which can be, for example, performing dental procedures;
3. It can be contraindicated for patients who have severe chronic respiratory insufficiency, concomitant use of central nervous system depressants, patients with kidney or liver disease, severe congestive heart failure, in pregnancy and during lactation. Therefore, there should be precautions for its use in these cases;
4. Advantageously, the benzodiazepines exhibit antagonist that reverses its effect from 1 to 2 minutes, flumazenil;
5. It is important that the dentist is able to use these drugs.

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