ORAL PREMEDICATION WITH BENZODIAZEPINES

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Abstract

Preoperative medication or premedication is the administration of medications before surgery, to reduce anxiety, which is common in these patients, and as prophylaxis of side effects of anesthesia like heart rhythm disorders, blood pressure variations, hypersalivation, etc. Benzodiazepines are the usual agents used in premedication to provide relief of anxiety, anterograde amnesia, and light sedation. The most common benzodiazepines used for premedication are midazolam, diazepam and lorazepam. They are usually given intramuscularly or orally in children. The time of use should be correlated with the moment of maximum effect depending on the method of administration. Time varies from twenty minutes for intramuscularly administered midazolam to two hours for peroral-administered lorazepam. The choice of a particular benzodiazepine, used for premedication, depends on its effects, duration of action, active metabolites, and side effects. The dose should be carefully tailored to provide the expected reduction of anxiety and light sedation and to avoid sleep and especially respiratory depression.

Keywords: premedication, benzodiazepines, oral administration, children

Introduction

The standard preoperative preparation of patients for anesthesia includes a visit during which the anesthesiologist reviews all medical documentation and talks with the patient about his health condition, medications and supplements the patient is using[1, 2]. The patient's physical examination is also performed to determine whether there is any risk factor for anesthesia and surgical intervention. Review of laboratory analyses and results of diagnostic procedures are important for risk assessment and decision-making about premedication and the most appropriate type of anesthesia. While examining the patient, the anesthesiologist assesses the both, mental and physical condition of the patient and makes a plan for preoperative preparation, premedication, anesthesia technique, and postoperative monitoring of the patient.

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Premedication involves the application of pharmacological agents to ensure adequate conditions for anesthesia[3]. There is no ideal drug or combination of drugs that will provide the best premedication.

Anesthesiologist prescribes premedication based on the patient's age, general condition, type of surgery that needs to be done, and available equipment for monitoring the patient after premedication. Explaining the whole procedure to the patient reduces anxiety and fear, which are present in 40-85% of patients before surgery[4, 5].

Premedication goals

The goals of premedication are reducing anxiety, providing sedation, analgesia, reducing secretion in the oral cavity and upper respiratory tract, blockade of the vagal reflexes, antiemetic effect, reduction of medications used for inducing anesthesia, amnesia and reduction of postoperative behavioral changes[2].

Medications used for premedication are numerous: benzodiazepines, anticholinergics, alpha 2 receptor agonists, opioids, ketamine, and antiemetics. Benzodiazepines are the usual agents used in premedication because they provide relief from anxiety, anterograde amnesia, and light sedation.

Administration of drugs can be oral, sublingual, nasal, rectal, intravenous, and intramuscular. Depending on the characteristics of the drug and the patient itself, we choose the most comfortable method of administration for the patient. Preoperatively administered drugs need to achieve

full effect before the patient arrives in the operating room, not after inducing anesthesia. Drugs that need to be taken by mouth should be given 1-1.5 hours before the patient arrives in the operating room with a water intake of a maximum of 150 mL[6].

Using benzodiazepines in premedication

Benzodiazepines have anxiolytic, sedative, amnestic, muscle relaxing, and anticonvulsant effects. They can also have a hypnotic effect if used in larger doses. As tranquilizers, benzodiazepines achieve their effect in the central nervous system (CNS), where they potentiate the effect of the main inhibitory neurotransmitter by binding to the specific benzodiazepine receptor - gamma-aminobutyric acid (GABA). Throughout this mechanism of action, they decrease neuronal excitability and, if used in appropriate doses, relatively selectively cause anxiolysis and amnesia, without respiratory depression[7].

Benzodiazepines can cause anterograde amnesia (when a person does not remember events that happened after the drug was administered). Among other beneficial effects, anterograde amnesia is one of the reasons benzodiazepines are often used as premedication drugs before surgery or other medical procedures that may be painful and/or unpleasant.

Oral administration of benzodiazepines has many advantages, including ease of administration, rapid action, as well as completely painless application of the drug, which is especially desirable in the pediatric population. They have a wide therapeutic index and a low incidence of toxicity. Reducing stress and fear improves the general condition of the patient and makes it easier for the medical staff to perform the necessary perioperative procedures, such as placing a peripheral venous line, setting up basic monitoring, etc, without complications[8, 9].

Premedication with oral benzodiazepines can be used not only before general endotracheal anesthesia (GETA) but also for interventions in regional anesthesia. The recovery time from local anesthesia with oral sedation can often be longer than from general anesthesia. If an oral agent is chosen for premedication, it must be administered early enough to achieve the desired effect at the desired time.

Monitoring during and after premedication is imperative for patients' safety. It involves monitoring vital signs like blood pressure, heart rate, and breathing to determine if the patient is stable and if vital signs are within normal limits. It is also important to assess the mental status because the patient can be drowsy or disoriented after taking benzodiazepines.

The most commonly used benzodiazepines in premedication

Benzodiazepines can be classified based on the length of their action as short time acting (midazolam), medium long time acting (lorazepam), and long time acting (diazepam). Short-time-acting benzodiazepines are usually used for procedural, short-term analgosedation, while medium and long-time-acting benzodiazepines are used for premedication in general anesthesia that will last up to several hours.

Diazepam is highly liposoluble, so it must be dissolved in organic solvents (propylene glycol, sodium benzoate), and its intravenous or intramuscular administration can be very painful. Phlebitis is a frequent consequence of intravenous diazepam administration, so oral administration, in a dose of 5-20 mg, is more acceptable (and more pleasant for patients). After oral administration, it is rapidly absorbed from the gastrointestinal tract[10]. The maximum effect of the drug occurs after 30 minutes to one hour in adults, and in children in 15-30 minutes. The duration of the effect is 2-4 h, but due to a long half-life (elimination half time 21-37 h), the presence of active metabolites and their accumulation can be longer (for example - elimination half-life of nordiazepam metabolite is 40-100 hours)[11]. Benzodiazepines bound highly to plasma proteins - albumins, so caution should be exercised in patients with hypoalbuminemia (liver cirrhosis, chronic renal failure) because the drug can have an enhanced effect. Diazepam metabolizes entirely by microsomal enzymes of the liver, and certain metabolites (oxazepam, temazepam) are active and can lead to prolonged sedation.

Lorazepam is a benzodiazepine anxiolytic that has a high affinity for benzodiazepine receptors in the brain. According to clinical trials, lorazepam is about 10-15 times more potent than diazepam in terms of the anxiolytic effect. This means that a lower dose of lorazepam is needed to achieve a similar effect as a higher dose of diazepam. It is applied orally, intravenously, or sublingually. Lorazepam intravenous administration is not associated with pain during the application nor with the occurrence of phlebitis. The oral dose of lorazepam for premedication is 1-1.5 mg, up to a maximum of 4 mg[12]. After a peroral application, due to lower liposolubility and thus slower penetration into the brain, the beginning of the action is slower compared to other benzodiazepines. The maximum effect is manifested in 30-60 minutes after the peroral application[13], while maximum drug concentration in the plasma is reached 2 hours after the peroral application[14]. Therefore, lorazepam is best administered *per os* 1.5-2 hours before surgery, so that the full effect is manifested before a patient enters the operating room. The duration of the sedative effect varies from 6-10 h and is therefore avoided in short-term procedures which require rapid awakening. It is also metabolized in the liver, but unlike diazepam and midazolam, doesn't have active metabolites, so it is recommended for use in elderly people and patients with liver diseases.

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Midazolam has a unique imidazole ring, which makes him soluble and stable in water and lipids, so it acts quickly and quickly metabolises[15]. It can be applied orally, intravenously, intramuscular, nasal, sublingual, or rectally. The effects are reducing anxiety, sedation, and amnesia. It has an increased affinity for benzodiazepine receptors, so it is 2 - 3 times stronger than diazepam. The dose is 0.2-0.5 mg/kg *per os*, and the maximum effect is expected 30-60 minutes after oral administration, while the maximum effect is expected in 20 minutes after intramuscular application. The intravenous or intramuscular application does not cause irritation or phlebitis. The frequency of side effects is small but should be used with caution because it can cause stronger sedation and respiratory depression, especially in elderly patients, or when combined with other drugs, depressors of the central nervous system[16]. It is usually given orally one hour before the introduction to anesthesia. The beginning of the action of midazolam is faster as well as the recovery, compared to diazepam, which is explained by better solubility of midazolam in lipids, faster distribution in peripheral tissues, and metabolic biotransformation. It is metabolized in the liver, producing an active metabolite - hydroxymidazolam, which is responsible for the potential for prolonged sedation. For this reason, it is recommended to prescribe the dose based on ideal body weight. The elimination half-time is 1-4 h and can be longer in older patients. Mental function usually returns to normal 4 h after application[17, 18]. Some drugs and food extend the effect of orally given midazolam (calcium blockers, erythromycin, grapefruit juice), while rifampicin, corticosteroids, anticonvulsants, and barbiturates show the opposite effect.

Midazolam has a special place in the premedication of children, where it is almost always administered orally in the form of syrup. The syrup has a sweet taste with fruit aromas and this makes it easier for children to drink it. One of the benefits of using midazolam in the form of syrup is its fast absorption[19]. The benefits of midazolam use in children, to other drugs, are rapid and efficient sedation and relatively short duration of action which allows the patient to quickly wake up and recover after the application of the drug, as well as anterograde amnesia afterwards[20].

There is a new, ultra-short-acting benzodiazepine - remimazolam, registered for the first time in January 2020 in Japan, then in 2021 in Europe, North Korea, China, and the USA. It is not yet registered in our country, but we can expect it soon because it has been increasingly used in procedural sedation and anesthesia in the adult population only, for now[21].

Other perioperative beneficial effects of benzodiazepines

Benzodiazepines, as one of the key groups of drugs in premedication, also have other favorable effects in the perioperative period. They can reduce oxygen and energy consumption and affects the level of the stress hormone, such as cortisol. Although oxygen consumption in the myocardium represents only 10-15% of the total body consumption of oxygen, it can be critical in patients with poor coronary reserve. Diazepam premedication reduces the metabolic response to perioperative stress, reduces cardiovascular response, and affects the immune system[22].

New recommendations for the prophylaxis of postoperative nausea and vomiting (PONV), strongly recommend the use of benzodiazepines for this purpose. Benzodiazepines, especially midazolam, and remimazolam, although not antiemetics, significantly reduce the frequency of postoperative nausea and vomiting in hospitalized and ambulatory patients, as shown by numerous studies and meta-analyses[23].

The use of benzodiazepines is mandatory when using a dissociative anesthetic - ketamine, to prevent the possibility of unpleasant dreams and delirium[24]. Ketamine and midazolam have a synergistic effect, and they are often used in combination for the analgosedation of patients during short-term procedures like dressing burns and orthopedic repositions in children. Midazolam reduces anxiety and stress, while ketamine provides analgesia and sedation.

Side effects and contraindications

There is no absolute contraindication for the use of benzodiazepines except for proven allergy, still, in some cases it is best to avoid them. Premedication with benzodiazepines is not recommended for patients with a history of drug and alcohol dependence, sleep apnea (because of possible breathing depression), liver and kidney failure, and pregnant and breastfeeding women (benzodiazepines cross the placenta and they are excreted in breast milk)[25].

Benzodiazepines can cause side effects like drowsiness, fatigue, dizziness, confusion, clumsiness, slurred speech, tremor, dry mouth, nausea, vomiting, headache, diarrhea, vision, and coordination problems. More serious side effects are delirium, paradoxical reaction (an increase of anxiety, excitement, aggression), blood pressure drop, and breathing depression.

Benzodiazepines are psychoactive drugs that can cause different effects on the nervous system, including delirium. Delirium is an acute and transient disorder of consciousness and attention characterized by hallucinations, disorientation, dyslexia, and cognitive and behavioral disorders. The mechanism of benzodiazepines causing delirium is not fully clarified, various neurotransmitters in the brain are involved, including GABA, glutamate, and dopamine. Delirium caused by benzodiazepines can be particularly pronounced in older patients and patients with neurological and psychiatric disorders. Therefore, caution is recommended when using benzodiazepines in these patients, as well as careful monitoring after administration of benzodiazepines.

After premedication with midazolam, a paradoxical reaction, and worsening of anxiety can occur. A paradoxical reaction represents an unusual reaction of the organism on this type of drug. Instead of the expected sedation and reduction of anxiety, there is an opposite effect, increased anxiety even aggression[26]. In case of overdose or excessive sedation, the specific antagonist is flumazeline in the dose of 0.01 mg/kg *iv* (intravenous), given in 15 seconds (maximum dose 0.05 mg/kg *iv*).

Conclusion

Oral premedication with benzodiazepines is an effective way to reduce anxiety and fear in patients preparing for invasive or diagnostic procedures, especially in children. They also lead to anterograde amnesia. They are relatively easy to use, dosing for oral use is simple and they act relatively fast. For the optimal oral application of premedication with benzodiazepines, it is important to carefully evaluate each patient and adjust the method of administration and dosage of the drugs according to their individual needs. The risk of side effects and complications, such as respiratory depression, muscle weakness, sedation, and loss of coordination, should be taken into account to minimize risks and ensure safe and effective administration. Premedication should be used with caution and under the supervision of medical personnel.

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