Anesthetic Agents Commonly Used by Oral and Maxillofacial Surgeons

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KEYWORDS

• Midazolam • Diazepam • Ketamine • Dexmedetomidine • Propofol • Nitrous oxide
• Anesthetic agents • Inhalational

KEY POINTS

- Thorough knowledge and understanding of an anesthetic agent's pharmacodynamic and pharmacokinetic profile are critical for safe and efficient clinical use.
- Short-acting drugs without active metabolites are ideal for providing the full spectrum of anesthesia in the unique office-based dental environment.
- To maximize satisfactory outcomes, selected anesthetic agents must match well with the needs of the patient, anticipated procedure, and surgeon.

INTRODUCTION

The oral and maxillofacial surgeon providing full-spectrum dental anesthesia services in the office-based environment currently has a multitude of anesthetic options available. In fact, this may be the dawn of a new "golden age of anesthesia" because of the novel agents and techniques being discovered that can quickly render a patient unconscious yet also provide an extremely fast and smooth emergence and recovery profile ideal for the unique dental environment. The multitude of options available today provide practitioners with great flexibility to create an individualized anesthetic plan, balancing the risks inherent with the patient's medical history and the anticipated surgical plan to achieve maximal results.

BENZODIAZEPINES: DIAZEPAM, MIDAZOLAM, REMIMAZOLAM

Since the discovery of chlordiazepoxide in 1957, benzodiazepines have had a strong presence in dental anesthesia, because of their relatively wide therapeutic index and low risk of producing unconsciousness and respiratory depression when administered alone at modest doses. It took time for the addictive profile of benzodiazepines to become apparent, after which rampant, unmonitored use was brought under further control and scrutiny. Nevertheless, benzodiazepines remain popular sedative and anxiolytic agents. There are currently dozens of available benzodiazepines that may be used for a multitude of purposes; however, a select few are more commonly used for anesthesia (Table 1).

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Table 1
Benzodiazepines

Initial IV dosing[a]	
Diazepam	2.5–5 mg
Midazolam	1–2 mg
Oral dosing	
Diazepam	2–10 mg orally
Midazolam	0.5 mg/kg; 20 mg maximum

[a] Titrated to desired effect.

Pharmacodynamics

Benzodiazepines all act as gamma-aminobutyric acid (GABA) -positive allosteric modulators, facilitating the ease at which GABA can bind to its own respective twin binding sites on neuronal chloride ion channels. What makes benzodiazepines unique is not the net increase in GABA activity or inhibitory neuronal activity, but rather the fact that they have their own binding site, called the benzodiazepine receptor, which is found on the gamma subunit of the chloride ion channel. When benzodiazepines bind to this benzodiazepine binding site, it causes a conformational shift in the spatial alignment of the subunits making up the chloride ion channel. The net result is an uncovering of one of the $GABA_A$ receptors, which permits GABA neurotransmitters easier access to their binding sites. Once both $GABA_A$ receptors are engaged and activated by GABA, the previously closed chloride ion channel opens, permitting the influx of chloride ions into the neuron, negatively hyperpolarizing the cell. Interestingly, to date there are no other known agonists for the benzodiazepine binding site; however, several other anesthetic agents do function in a similar fashion producing $GABA_A$-positive allosteric modulation albeit via alternative binding sites. In addition, benzodiazepines have the added benefit of a competitive antagonist, flumazenil, which is capable of reversing the activity of benzodiazepines.

All benzodiazepines produce dose-dependent central nervous system (CNS) depression ranging from anxiolysis to general anesthesia. Benzodiazepines are capable of producing anterograde amnesia, although this effect can be variable and should not be guaranteed. Despite the fact that benzodiazepines cause global CNS depression, they have also been known to cause paradoxic excitatory reactions in some patients, with the highest risk associated with extremes of age. From a cardiovascular and respiratory standpoint, benzodiazepines tend to be rather safe when used alone in modest doses. A minimal reduction in systemic vascular resistance may be appreciated, which is mainly attributed to the anxiolytic effects and decreased sympathetic outflow. Benzodiazepines cause minimal depression of the respiratory drive, especially when given as a solo agent. However, this safe profile is ablated when used concurrently with other CNS depressant drugs producing synergistic or additive effects. Benzodiazepines also produce centrally mediated skeletal muscle relaxation, which can contribute to collapse of the airway musculature, upper airway obstruction, and loss of airway patency.

Pharmacokinetics

The pharmacokinetics of benzodiazepines depends not only on the specific agent but also the route of administration, with the onset speed being the fastest in parenteral routes, followed by the considerably slower enteral routes. Benzodiazepines are metabolized hepatically, typically via a variety of agent-specific cytochrome p450 enzymes, most commonly the 3A4 or 2D6 isozyme variety.[1]

Diazepam notoriously has several active byproducts, all of which can significantly extend the duration of action such that a "hangover" effect may persist for days. The longest is desmethyldiazepam, which has an elimination half-life approximating 36 to 200 hours.[1] Oxazepam and temazepam, 2 of its other active metabolites, are benzodiazepines as well and can persist for considerable lengths of time. Midazolam has an active metabolite, α-hydroxymidazolam; however, its short half-life makes it clinically insignificant. Diazepam and midazolam can be administered enterally or parenterally. As enteral agents, they are subject to first pass hepatic metabolism as well as the modulation effects concurrently found with CYP450 isozyme inhibitors or inducers. Remimazolam is an ultra-short-acting benzodiazepine currently in phase 3 clinical trials, but is likely to play a significant role in office-based anesthesia in the near future. It is metabolized via tissue esterases, rather than undergoing hepatic metabolism, and has the added benefits of lacking active metabolites or accumulating in the peripheral tissues. Its pharmacokinetic profile essentially mimics that of remifentanil, only exerting activity for $\sim$5 to 10 minutes before all effects begin to wane completely. Theoretically, such a drug could be used to thoroughly sedate a patient, only to have them recover completely in an extremely short period of time. Remimazolam is worthy of attention with regards to future trends in ambulatory anesthesia.

Clinical Use

Diazepam can be given orally to reduce preoperative anxiety either the night before or an hour before the patient's appointment. Avoidance of any other CNS depressant medications is recommended for