



The Use of Midazolam Hydrochloride Continuous Infusions in Palliative Care

Question: What considerations should be taken into account for patients who will receive midazolam hydrochloride continuous infusion on an acute care unit?

Answer: Midazolam hydrochloride (MDZ) (Versed®, Roche Laboratories, Nutley, NJ) is a very short-acting benzodiazepine (BDZ), originally released as an induction agent for general anesthesia and to provide conscious sedation during brief diagnostic procedures. In the oncology setting, MDZ has been used intermittently for short-term effect to ease the discomfort of procedures such as endoscopy or bone marrow biopsy. More recently, MDZ has been used continuously as an adjuvant agent in pain management (in combination with an opioid or other agents) or to provide total sedation at the end of life.

Mechanism of Action and Pharmacokinetics

MDZ is classified as a BDZ; other well-known medications in this class include diazepam, lorazepam, and clonazepam. All BDZs have anxiolytic, muscle relaxant, sedative-hypnotic, anticonvulsant, antiemetic, and amnesic effects. As with all BDZs, the mechanism of action of MDZ is through binding to gamma aminobutyric acid receptors in the central nervous system (CNS), leading to CNS depression. MDZ is the shortest-acting medication within the BDZ class, with the onset of action three to five minutes after IV injection, and it is twice as potent as diazepam in comparable doses. The drug is metabolized by the liver and excreted in the urine. The half-life is one to four hours (Clinical Pharmacology, 2000). These qualities make MDZ an ideal parenteral BDZ because it is easy to titrate and has a rapid onset and short duration once the infusion is discontinued.

Uses of Midazolam in Oncology and Palliative Care

Continuous infusions of MDZ have two primary uses in oncology and palliative care. First, MDZ is an effective adjuvant when combined with opioids for the management of pain associated with significant anxiety. A second use for MDZ in this setting is to pro-

vide total sedation for the relief of uncontrolled physical and emotional symptoms such as dyspnea, delirium, nausea, vomiting, myoclonus, seizures, psychological and spiritual distress, or "terminal agitation" sometimes experienced during end-of-life care (Fainsinger et al., 2000). Previously referred to as "terminal sedation," the term "total sedation" is preferred by palliative care experts and end-of-life organizations, including the National Hospice and Palliative Care Organization (NHPCO), as this term addresses complete relief of suffering (Committee on Ethics of the NHPCO, 2001).

Sources of pain and suffering are multifactorial. Often, people coping with chronic cancer pain experience significant anxiety along with pain. In the presence of anxiety, pain can escalate requiring higher doses of opioids, thereby increasing the risk of significant side effects such as sedation, confusion, and myoclonus (Berger et al., 2000). The addition of an anxiolytic allows better symptom management of anxiety and pain with lower doses of opioids, resulting in fewer opioid-induced side effects.

Total sedation is the provision of care for patients with advanced disease to ease overwhelming and unrelieved physical, emotional, or spiritual distress. This palliative therapy is provided only to patients who no longer wish to be aware (Fine, 2001). The literature reveals that the use of total sedation is uncommon and yet effective for the treatment of intractable suffering (Fine). BDZs, as a class, are effective and appropriate agents for the inducement of total sedation.

Ethical Considerations in the Use of Midazolam for Total Sedation

Much has been written in the medical and legal literature about the ethical appropriateness of total sedation for the relief of suffering at the end of life. The intent of total sedation is the achievement of maximum symptom relief with minimal medication side effects. When medications such as BDZ and opioids are administered skillfully, death is neither hastened nor prolonged and ultimately occurs because of the underlying disease processes (Education for Physicians on End-of-Life Care Project Team, 1999). Guidelines have been published that state indications for the implementation of this intervention (Committee on Ethics of the NHPCO, 2001). Obviously, the decision to implement treatments that are as significant

and potentially irreversible as total sedation is a process that occurs within the context of a particular patient's illness and goals of care. Although all patients have the ethical right of autonomy (i.e., the right to determine their own treatment), the decision-making process must include full informed consent and input from each person touched by the outcome of the treatment. In most cases, this would include patients' immediate family members or significant others, the healthcare team, and members of the administrative team at the hospice or hospital where total sedation is to be administered. Careful consideration needs to be provided for patients who are suffering from unrelieved symptoms at the end of life and have limited decision-making capacity. Additionally, great care must be given to ensure that every effort has been made to alleviate patients' physical, emotional, and spiritual suffering prior to instituting total sedation (Cherny & Portenoy, 1994). As with all palliative care, patients and family members must be treated with dignity and without a sense of abandonment by their healthcare providers. Finally, Fine (2001, p. 82) summarized the importance of this process as "all those involved with the patient must understand and be confident in the 'correctness' of the decision to provide total sedation to prevent retrospective second guessing, remorse, or more egregious conflicts."

Administering Midazolam

Routes of administration: MDZ has properties that make it a versatile and effective medication to administer. MDZ is available in liquids and tablets that may be administered orally or rectally and in sterile solution for parenteral or rectal administration. MDZ tablets or parenteral solutions may be inserted into the rectum with good efficacy, using the same dosing as the oral route. MDZ is well absorbed via IV or subcutaneous routes (Kline, 2002). Although the IV route provides the most rapid route for drug delivery, it requires IV access, something that can be difficult to establish and maintain in end-of-life care (Paice & Fine, 2001).

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