

Sedation in the Intensive Care Unit: An Overview

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ABSTRACT

Sedation in the critically ill patient is essential to ensure maximal quality of life in the high-stress environment of the intensive care unit. The main goals of sedation include augmentation of pain control, management of agitation and psychological distress, and improvement of patient tolerance and acceptance of the endotracheal tube and ventilatory support. Ideally, the sedated patient should be asleep yet easily rousable. This is most commonly achieved in practice with a combination of morphine and benzodiazepines although a variety of combinations of drugs have been utilized. Other agents which have been employed include, other opiates such as fentanyl and sufentanil, butyrophenones such as haloperidol, and anesthetics such as propofol. These agents will be reviewed with respect to their role in sedating the critically ill patient.

Key Words: benzodiazepine, critical care, opiates, sedation.

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RÉSUMÉ

La sédation, chez le patient dont l'état est critique, est essentielle pour lui assurer une qualité de vie maximale dans le milieu très stressant qu'est l'unité des soins intensifs. Les principaux objectifs de la sédation comprennent le soulagement accru de la douleur, la maîtrise de l'agitation et de la détresse psychologique, et une meilleure tolérance et acceptation par le patient de l'intubation endotrachéale et de la ventilation assistée. Idéalement, le patient sous sédatifs devrait dormir mais pouvoir être facilement réveillé. Dans la pratique, on réussit couramment à atteindre cet équilibre en associant de la morphine à une benzodiazépine, bien qu'une foule d'autres associations médicamenteuses soient employées. Parmi les autres médicaments utilisés on note les autres opiacés comme le fentanyl et le sufentanil, les butyrophénones comme l'halopéridol et les anesthésiques comme le propofol. Ces agents seront examinés relativement à leur rôle dans la sédation des patients dont l'état est critique.

Mots clés : benzodiazépines, opiacés, sédation, soins intensifs.

For the Intensive Care Unit (ICU) patient, the constant activity, lights and alarms, in addition to the impedance of normal sleep patterns may result in the phenomenon referred to as ICU agitation. The agitation frequently manifests as disorientation and impaired short-term memory. It ranges physically from mild restlessness to violent, aggressive, combative behaviour with possible detrimental outcomes in the clinical management of the patient. Anxiety may be the direct result of pain or alteration in respiratory and metabolic homeostasis. The ICU patient will often experience a variety of these.^{1,2}

Assessing the need for sedation in this type of patient is difficult based on objective analysis of the literature.

There are anecdotes from medical personnel who had spent time in an ICU and who recounted sensations of pain, anxiety, and disorientation.³ As well, one investigator interviewed 60 patients after discharge from the ICU with respect to their recollections of their stay. Although memory recall of the early part of their admission to the ICU was poor, experiences describing pain, anxiety, lack of rest, and paralysis were frequently recalled during the latter portion of their stay.⁴ Objective analysis of the level of sedation is often based upon alterations in the patient's hemodynamic indices reflecting increased sympathetic activity during various procedures but this may be inaccurate due to the possibility of interference

from concurrent disease states and medications administered.⁵

Intensive Care Unit patients require sedation to provide varying degrees of analgesia, anxiolysis, amnesia and respiratory depression. The level of sedation required is dependent upon the severity of the patient's condition and the intensity of treatment that will be required.³ As there are no known good, physiological endpoints with quantitative measures to assess the level of sedation, administering sedative agents effectively may be problematic. In the past there has been a trend towards oversedation to guarantee patient comfort and cooperation. Oversedation is associated with a number of risks such as hypotension, bradycardia, venous

stasis, muscle wasting, risk of compression injuries to peripheral nerves, respiratory depression with subsequent weaning difficulties, and coma.⁵ Undersedation, on the other hand, may result in patient discomfort, pain, hypertension, tachycardia, and hyperventilation.⁶ The more recent trends in sedation aim for the patient to be sleepy yet easily rousable. Complete anaesthesia is reserved for a subset of patients with tetanus, oxygenation difficulties or head injuries.^{4,5}

The need for sedation may be influenced by environmental factors. Every effort should be made to empathize with the patient, normalize daily routines, and explain procedures that are being performed. The presence of a television or radio also helps orient the patient. Benzodiazepines, opiates, and anaesthetics used alone or in combination remain the cornerstone for sedating the ICU patient and are reviewed in this paper. As well, while many intubated patients will also receive neuromuscular blockers to facilitate ventilation a discussion of these agents is beyond the scope of this paper. A review of these agents has recently been published in the *Journal*.⁷

Benzodiazepines, with their sedative and anxiolytic effects, have replaced the traditional barbiturate or neuroleptic for general sedation in the ICU setting.⁵ They enhance the activity of neurotransmitter GABA in the hippocampus, thalamus and hypothalamus thereby inhibiting the release of norepinephrine and serotonin resulting in central nervous system (CNS) depression, anxiolysis, and amnesia.⁸ The selection of benzodiazepine used will depend upon the strategy for sedation designed for each individual patient. Long-acting benzodiazepines, such as diazepam with an elimination half-life of one to two days, would be ideal for the patient who is anticipated to require continual sedation for a prolonged period. Lorazepam, with its half-life of

approximately 20 hours, is a shorter-acting alternative to diazepam.⁶

Midazolam, also a benzodiazepine, possesses some unique properties. The injectable solution is formulated at a pH of 4 which allows reversible opening of the diazepam ring between position 4 and 5. Improved water solubility thereby reduces the risk of thrombophlebitis compared to parenteral diazepam when given peripherally. At physiologic pH, the diazepam ring is closed increasing lipophilicity and passage through the blood brain barrier. The onset of action ranging between 30 and 60 minutes is not significantly different from diazepam's onset of 45 to 60 minutes however, the half-life of midazolam is substantially shorter.^{9,10} Redistribution of benzodiazepines from the CNS is responsible for the termination of effect following single doses of midazolam and diazepam. In this situation, recovery from midazolam is not faster than from diazepam despite the shorter half-life of midazolam.¹¹ However, with repeated dosing there may be a potential difference in favour of midazolam although studies are required to confirm this. Even with midazolam prolonged continuous use may lead to accumulation and prolonged sedation.¹⁰ Midazolam is administered by infusion ranging from 0.3 to 3 mcg/kg/minute. Therapeutic equivalency of midazolam to diazepam is difficult to assess but it is estimated that midazolam is approximately three times more potent on a milligram to milligram basis.¹⁰

Two hundred and forty-nine cases, utilizing midazolam by continuous infusion in ICU patients for up to 11 days, found no significant alterations in cardiovascular or respiratory status secondary to midazolam use. It was noted that even though midazolam is reported to undergo hepatic metabolism to inactive hydroxy-metabolites, ICU patients and the elderly exhibit a longer duration of effect.^{5,9} There is some suggestion that midazolam

exhibits tachyphylaxis with continual use but further controlled studies are required.^{10,11} With respect to the existence of withdrawal reactions secondary to midazolam discontinuation, there is much conflicting data and the information which does exist is confounded by subjective assessments, concurrent medications and concurrent weaning from the ventilator. Each patient should therefore be monitored closely. Midazolam has a more pronounced amnestic effect than other benzodiazepines which may be beneficial in the critically ill patient.^{14,15}

Although there are no pharmacoeconomic studies to date, it has been suggested that midazolam, though having higher actual acquisition costs, could reduce the time to wean a patient from ventilatory support and decrease stay in ICU with overall economic saving but studies are required. This lack of information may be the limiting factor supporting the conversion from diazepam to midazolam in many centres.

A benzodiazepine is most commonly combined for synergistic sedative effects with an opiate such as morphine, fentanyl, or sufentanil. Morphine, the standard for opiates, provides analgesia by altering the perception of pain centrally. Sedation is a result of altered sympathetic and vagal activity. This also results in bradycardia and vasodilation. By suppressing the medullary cough centre, morphine provides antitussive activity thereby improving tolerance of the endotracheal tube. It is most commonly prescribed in bolus doses of one to fifteen milligrams every one to four hours. A continuous infusion of 2-3 mg/hr is also effective. Morphine, which is relatively inexpensive, is easily titratable to effect and easily reversed with an antagonist such as naloxone.³

The synthetic opiate analgesics such as fentanyl, sufentanil, and alfentanil differ from morphine primarily in their affinity and activity

at the mu receptor and in their pharmacokinetics (Table I).¹⁶ The actual duration of action for these agents is much shorter than the elimination half-life due to redistribution from the central compartment. As these are lipophilic compounds, accumulation may occur with continued use. Some of the main advantages of these agents over morphine include the relative absence of cardiovascular effects and the easy on/off titratability with the use of an infusion.¹⁷ A major disadvantage is the lack of studies specifically addressing their use in the ICU for sedation. As the major route of elimination of these agents is hepatic, adjustment of the dose in patients with concurrent renal dysfunction does not appear to be necessary. Alterations in plasma protein binding associated with renal dysfunction however, may alter the free fraction of drug.¹⁷ Although relatively uncommon, respiratory depression and skeletal muscle rigidity may occur. Sufentanil has been associated with lowering the seizure threshold in some patients.¹⁸

The synthetic opiate analgesics are significantly more expensive than morphine, prohibiting routine use of these agents in ICU patients for sedation. These agents may be indicated for those patients not controlled on adequate doses of morphine.

Propofol, an intravenous hypnotic used for induction of anaesthesia is becoming increasingly popular for sedation in the ICU.¹⁹ The dose-dependent depression of the CNS appears to be the result of propagation of GABA transmission by binding to a specific receptor site independent of the benzodiazepine receptor site.²⁰ With the administration of propofol, the cerebral metabolic rate, perfusion pressure, and intracranial pressure are decreased.²¹ Cardiovascularly, propofol reduces sympathetic outflow from the brain stem and depresses the baroreceptor response thereby making it advantageous for those patients with

Table I¹⁶ Pharmacokinetic Properties of Synthetic Opiates

Parameter	Agent		
	Fentanyl	Sufentanil	Alfentanil
Potency (Morphine = 1)	50-100	250-1000	5-10
Volume of Distribution (L/kg)	2-3	1.7-2.5	0.4-1
Clearance (ml/kg/min)	11.6	12.7	6.4
% Nonionized at pH 7.4	9	8.5	89

coronary artery disease.²² Propofol suppresses the respiratory drive in subhypnotic doses.²³

Propofol pharmacokinetics follow a three compartmental model with onset of action in less than one minute and duration of action less than 15 minutes.²⁴ Recent literature indicates that propofol dosing need not be adjusted in hepatic or renal dysfunction. There has been a trend towards prolongation of effect when used in patients with renal dysfunction, but clinically this has not proven significant.^{25,26} Propofol has been administered at a rate of 20-60 µg/kg/min to maintain sedation in ICU patients.²⁷

Propofol is indicated as an alternative to a benzodiazepine/narcotic combination for short-term sedation. It may also be useful for those patients not responsive to more traditional methods of sedation. Cost is a significant deterrent for extensive use for general sedation in the ICU setting.

Haloperidol, with its large therapeutic index and one to five minute onset of action, is effective for the management of acute agitation within the ICU. Doses range from 0.5 to 5 mg per dose initially given every 15 to 30 minutes until the desired effect is achieved. The main dose-limiting adverse effect is hypotension.

In conclusion, many new agents are being introduced and promoted in the ICU for management of sedation in the patients. Midazolam, because it can be administered by infusion, would seem to have a potential benefit in terms of shorter half-life in patients who require repeated doses

for sedation. But more study is required to confirm a pharmacoeconomic benefit given the higher acquisition cost of midazolam. For short-stay patients requiring infrequent, intermittent dosing there does not appear to be any advantage of midazolam over diazepam. The newer synthetic opiates offer few advantages to warrant their use as first line agents over the inexpensive morphine. Fentanyl is a reasonable alternative to morphine in those patients who are unresponsive and who have had an adequate trial of morphine. At present there are clinically insignificant advantages to warrant the extra expense associated with the use of sufentanil and alfentanil for sedation in the ICU patient. Haloperidol still remains an inexpensive and effective means of sedating the ICU patient. ☒

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