A Case for Dexmedetomidine

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The use of sedative and analgesic agents is an essential component to the care of critically ill patients who are prone to agitation and delirium caused by various factors, including mechanical ventilation, procedures such as bronchoscopy and central venous cannulation, and underlying illnesses. These states can lead to an unsafe patient environment and untoward hemodynamic effects, possibly increasing the difficulty of providing patient care. Indeed, delirium has been shown to be associated with increased morbidity and mortality rates.1 The goal of sedation and analgesia is to provide a comfortable state for the patient – one that is free of pain and anxiety – without causing adverse cardiovascular, respiratory or neurologic effects. As with any treatment, the choice of sedative or analgesic agent must be tailored to the individual patient.

Dexmedetomidine hydrochloride, approved in 1999 by the Food and Drug Administration (FDA) for use in patients receiving mechanical ventilation for up to 24 hours, is a relatively new agent with unique properties that may make it an interesting and useful choice for sedation in the intensive care unit.

Dexmedetomidine is an imidazole compound that exerts its effect by selective α2-adrenergic receptor agonist action and is eight times more specific for these receptors than clonidine. The sedative and analgesic effects of the drug appear to be mediated by postsynaptic α2-agonist activity in the locus caeruleus. Its major cardiovascular effects – hypotension and bradycardia – seem to occur by both central sympatholysis in the locus caeruleus as well as by peripheral inhibition of norepinephrine release at nerve endings. The drug also has a potential hypertensive effect, which is mediated by a subtype of the α2-receptor found on the smooth muscle cells of resistance vessels whose activation leads to vasoconstriction. The pharmacokinetics of dexmedetomidine include a half-life of distribution and elimination of 5 to 10 minutes and 2 hours, respectively, and a volume of distribution of 1.3 L/kg. About 94% of the drug is protein-bound to both albumin and α1-glycoprotein. It is metabolized in the liver to inactive methyl and glucuronide conjugates that subsequently are eliminated by renal excretion. Hepatic insufficiency causes a several-fold increase in the half-life of elimination.2,3,4

Several unique pharmacologic properties often are cited as the reason why dexmedetomidine may be a more desirable drug than the traditional choices in critically ill patients. Most notably, these include a unique style of sedation, analgesic actions, and apparent lack of respiratory depression. With regard to its anxiolytic properties, dexmedetomidine has been shown to provide adequate, deep sedation as judged by the Ramsay sedation score (RSS), without changing attentiveness as judged by the critical flicker fusion (CFF) threshold. During this latter test, the frequency at which healthy individuals sedated with dexmedetomidine first see a flickering light source as a fused line is no different than that of placebo-treated controls. This property produces sedation at a higher bispectral index (BIS) monitor score creating an environment where a patient can be aroused to participate in care, such as a neurologist exam or in weaning trials, and then allowed to return to sleep when desired.2,5  Dexmedetomidine also possesses analgesic qualities that likely are mediated by receptor agonist activity in the spinal cord. In clinical studies, patients treated with dexmedetomidine have been shown to require up to 50% less morphine, potentially decreasing the incipient side effects of narcotics such as constipation, altered mental status and histamine release. There also is evidence that administering dexmedetomidine to healthy individuals has a minimal effect on minute ventilation and no deleterious effect on oxygen saturation. In theory, analgesic-sparing properties make the drug capable of providing sedation and analgesia without inhibiting respiration, allowing for more expedient weaning from mechanical ventilation and for sedation both during and through the potentially hemodynamically stressful period of extubation.6,7

In clinical studies, the efficacy of dexmedetomidine sedation has been compared to placebo by assessing each group’s need for rescue sedation with either midazolam or propofol and for rescue analgesia with morphine sulfate to maintain either a similar BIS or RSS. A typical regimen in several of the clinical studies includes administering a
bolus infusion of 1 µg/kg of dexmedetomidine, followed by an infusion of 0.1 to 0.7 µg/kg/h for up to 24 hours. The available studies certainly seem to demonstrate that the rescue dose of sedative and analgesic agents is significantly decreased in the dexmedetomidine groups compared to the placebo-treated groups, suggesting that the α2-agonist is effective at providing sedation and even lowering the narcotic requirement in critically ill post-surgical patients.6-9 However, it must be noted that the reduction in these two groups does not replace clinically relevant endpoints and other markers of outcome, which have yet to be studied extensively. While dexmedetomidine may achieve sedation and some amount of analgesia, it is not clear whether its use is associated with any decrease in adverse events such as respiratory depression and oxygen desaturation.

As with any drug therapy, there are potential adverse reactions associated with dexmedetomidine which may make other choices, such as propofol, benzodiazepines, and narcotics, more appropriate. Given its mechanism of action, dexmedetomidine has been associated with severe bradycardia and cases of sinus arrest. Hypotension also occurs in up to 30% of patients and therefore this drug should be used with caution in patients who may not tolerate these hemodynamic events. While these events are more likely to occur during bolus administration, they are not insignificant during the infusion period. In addition, as with clonidine, there is potential for tolerance and withdrawal. 2,3,10

Dexmedetomidine is a novel and distinct sedative and analgesic agent that offers unique advantages in critically ill, mechanically ventilated patients, such as a potential decrease in narcotic-induced respiratory depression and an interactive, cooperative style of deep sedation. However, these potential advantages must be tempered against the known potential adverse hemodynamic reactions and the fact that clinical outcomes, such as mortality rates, intensive care unit length of stay, and time to extubation, have yet to be studied. In addition, the drug’s safe use as a long-term infusion has yet to be studied. Certainly, this agent may be an excellent choice for sedation in select patients, and further investigation into its potential uses is warranted.

References