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Dexmedetomidine Prevents and Treats Agitation, Delirium, and Withdrawal

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Learning Objectives: 1) To recognize the signs, symptoms and detrimental effects of agitation, delirium, and withdrawal. 2) To describe how dexmedetomidine prevents and treats agitation, delirium, and withdrawal.

Abstract

Agitation, delirium, and withdrawal present challenges to the health care provider. Agitated, delirious, or withdrawing patients may injure themselves and/or be ineffectual in assisting in their own care, providing a hindrance to their healing. Trauma patients are at particular risk for wound disruption and further injury in this setting. Dexmedetomidine prevents and treats agitation, delirium, and withdrawal and is poised to become a strong part of the clinician's armamentaria in caring for these patients.

Agitation is a frequent and challenging problem in the perioperative and intensive care unit (ICU) patient care. Contributing factors include underlying illness, pain, anxiety, and delirium. Agitation can result in dangerous consequences ranging from poorly tolerated invasive therapy to self-destructive behavior. Sedatives are often administered to facilitate care of agitated patients. Nevertheless, multiple pharmacologic agents are typically administered during perioperative and ICU care, and may result in significant and often unpredictable outcomes, even leading to or worsening agitation and confusion. Contributing agents include benzodiazepines, opioids, volatile anesthetics, anticholinergics, antibiotics, and muscle relaxants. These medications may interact unpredictably, leading to difficult patient care situation, particularly in the elderly patient. Frequently, the effects of these drugs are not related to the medication itself, but rather to multiple metabolites with varying rates of degradation and excretion.

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Dexmedetomidine, a selective α_2 -adrenergic receptor agonist, exhibits sympatholytic, sedative, and analgesic effects. It acts at presynaptic and postsynaptic adrenergic sites. Dexmedetomidine inhibits the release of norepinephrine and terminates the propagation of pain signals by activation of the presynaptic α_2 -adrenoceptor. Additionally, dexmedetomidine inhibits sympathetic activity with a resultant decrease in blood pressure and heart rate by postsynaptic activation of these receptors in the central nervous system. Together, these effects produce sedation, anxiolysis, sympatholysis, and analgesia.¹ Although dexmedetomidine may be initiated with a loading dose of 0.5 mcg/kg infusion during 10–20 minutes, more commonly, therapy begins with a modest infusion of 0.3–1 mcg/kg/hr titrated to the desired effect.

Dexmedetomidine has several advantages over traditional medications such as narcotics, benzodiazepines, or propofol for use as a sedative in the ICU. Dexmedetomidine produces minimal respiratory depression, which facilitates sedation in the nonintubated patients and allows extubation without the need to discontinue the drug infusion. Dexmedetomidine sedation may be continued during the postextubation period, providing flexibility in the timing of tracheal extubation and making the drug useful during the ventilator weaning process. A further advantage of dexmedetomidine is relative ease of arousability in the treated patients, i.e., they can typically be calmly and easily awakened, facilitating ease of patient evaluation and care. Additionally, patients receiving dexmedetomidine demonstrate a lower sympathetic tone. Dexmedetomidine has been described to be effective in treating four patients with agitation and hyperadrenergic states refractory to haloperidol.² Elevated sympathetic tone contributes to morbidity and mortality in the trauma patient and is an additional problem in caring for the agitated and/or delirious patient.

In view of these attributes, dexmedetomidine may be of great benefit in treating and preventing agitation and delirium in perioperative and ICU patient care. Additionally, dexmedetomidine may be a useful additional tool in a number of other trauma situations that may cause agitation and confusion, such as traumatic brain injury.

Withdrawal Symptoms

Withdrawal symptoms from benzodiazepines or narcotics occurs not infrequently in trauma and ICU patients. In addition to those who experience withdrawal from medications taken at home, including alcohol and illicit drugs, some may withdraw from medications initiated in the hospital or ICU. This is particularly true for those receiving high dosages of benzodiazepines or narcotics over prolonged periods. Symptoms and signs of withdrawal include agitation, hypertension, tachycardia, and diaphoresis. These symptoms may easily be overlooked because of their similarity to other manifestations of critical illness. The majority of these hyperadrenergic-state withdrawal symptoms can be relieved by dexmedetomidine.

Ethanol withdrawal symptoms are frequently managed with benzodiazepines or even intravenous ethanol. Dexmedetomidine was shown to be as effective as diazepam in relieving the ethanol withdrawal reaction in rats.³ Compared with placebo, administration of dexmedetomidine diminished the severity of the ethanol withdrawal reaction as measured by the sum score of the three most specific withdrawal signs (rigidity, tremor, and irritability) in ethanol-intoxicated rats.⁴ Interestingly, dexmedetomidine has also been shown to relieve ethanol-induced neuronal loss in the locus ceruleus.⁵ Votava et al⁶ tested in rats whether dexmedetomidine inhibits behavior uniformly or with respect to particular stimuli or situations. They found a dose-dependent, antiaggressive effect in

aggressive mice. Nonetheless, while dexmedetomidine has been shown to be effective in such setting in rats, its effectiveness at treating or preventing delirium tremens in humans has not been fully elucidated, and therefore, while promising as a component in the care of withdrawal of the patient with alcohol and/or benzodiazepine dependency, particularly regarding the hyperadrenergic state, dexmedetomidine cannot be recommended to be the sole agent for these patients at this time.

In humans, dexmedetomidine has been reported to be useful in preventing and treating drug-withdrawal symptoms. Maccioli⁷ has reported using dexmedetomidine to treat severe withdrawal symptoms in two ICU patients. One of these patients was a cocaine addict who was effectively sedated with dexmedetomidine. The patient's clinical symptoms improved immediately following the loading dose (1 g/kg). The second patient was successfully treated with dexmedetomidine for 7 days for his narcotic/benzodiazepine withdrawal symptoms. In a double-blind, randomized, and comparative parallel-group study design, dexmedetomidine premeditation was further found to attenuate ketamine-induced postanesthetic delirium. Compared with midazolam, dexmedetomidine proved to have equal sedative and anxiolytic effects after intramuscular administration.⁸ Moreover, dexmedetomidine elicited significantly less preoperative psychomotor impairment and less anterograde amnesia than midazolam. Additionally, dexmedetomidine was more effective in reducing adverse ketamine-induced central nervous system effects.

Dexmedetomidine has also been reported to attenuate withdrawal symptoms in pediatric patients. Finkle and Elrefai⁹ reported using dexmedetomidine infusion to "detoxify" a 13-kg infant with Hunter syndrome who was sedated for a prolonged time with opioids and benzodiazepines. Additionally, Tobias et al¹⁰ reported using dexmedetomidine successfully in treating a 17-year-old patient who developed withdrawal symptoms in the ICU.

Emergence Delirium

Emergence delirium (ED) is a frequent challenge in caring for the postoperative pediatric patient recovering from general anesthesia (GA). A variety of medications has been suggested for the treatment/prophylaxis of ED with varying degrees of success.^{11–13} Guler et al¹⁴ administered dexmedetomidine (0.5 mcg/kg) to children 5 minutes before extubation following tonsillectomy. They found that children experienced smoother emergence from GA with better pain scores when compared with the placebo group. They also noted a lower frequency of airway difficulties, which they attributed to the lessened degree of laryngeal stimulation as a result of the sedative and analgesic effects of dexmedetomidine. In a similar study, Ibacache et al¹⁵ compared a smaller dose of dexmedetomidine (0.3 mcg/kg) administered at the beginning of the procedure to placebo and found a smoother emergence from GA. These pediatric studies used bolus doses of dexmedetomidine without an infusion and reported stability in the subjects' vital signs during the administration of the drug.

Another study compared the effects of dexmedetomidine infusion (0.2 mcg/kg/h) to a placebo saline infusion on ED in children aged 1 to 10 years.¹⁶ The infusion was started within a few minutes following the induction of GA and was continued through the procedure. The trachea was extubated at the end of the procedure. The infusion of dexmedetomidine was terminated 15 minutes following the postanesthesia care unit admission. Using a blinded observer and compared with the placebo group, the incidence and frequency of ED was lower in the children who received dexmedetomidine. On the other hand, the times to extubation or discharge were the same. A loading dose was not

administered. Dexmedetomidine infusion was safe, with all the patients maintaining stable vital signs. Dexmedetomidine reduces norepinephrine release and sympathetic activity, which may explain its role in achieving superior sedation and preventing ED.¹⁷

Conclusion

Dexmedetomidine needs to be studied further with respect to its properties as a sedative and its side effect profile as many of the examples provided in this discussion are the result of either case reports, retrospective evaluations, or anecdotes. For example, the pharmacokinetics and pharmacodynamics of the drug are as yet undescribed in the pediatric population. Furthermore, the safety profile for a dexmedetomidine infusion longer than 24 hours is only beginning to be elucidated. Appropriate patient selection remains important, with patients already having either a low tone state or hypovolemia being relatively excluded from dexmedetomidine use, given its sympatholytic effect.^{18,19} Dexmedetomidine is a promising agent in preventing and treating agitation, delirium, and withdrawal while providing a comfortable, cooperatively sedated patient.

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