Should Dexmedetomidine Replace Benzodiazepines as the Preferred Sedative, as Suggested by New Guidelines from the Society for Critical Care Medicine*?

THE "PRO" SIDE

Over the past decade, most Canadian intensive care units (ICUs) have adopted locally developed standardized protocols for delivery of analgesics and sedatives to patients who are undergoing mechanical ventilation to alleviate pain, anxiety, and agitation. Although I do acknowledge the benefits of protocolized care, not all patients have the same needs with respect to sedation and analgesia, so one of the consequences of this "checkbox" approach is oversedation caused by unnecessary drug exposure in many patients.[1] This year, the American College of Critical Care Medicine published clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU.[2] These guidelines, which update the decade-old previous guidelines, recommend lighter levels of sedation for these patients (grade +1B [strong recommendation, supported by moderate evidence, favouring the intervention]) and avoidance of benzodiazepines (grade +2B [weak recommendation, supported by moderate evidence, favouring the intervention]). However, if benzodiazepines are removed from the pharmacological arsenal, only narcotics, propofol, and dexmedetomidine remain in terms of drugs that have anxiolytic or sedative properties and that are predictably titratable. Purposely avoiding the terms "never" and "always", I would agree that the utility of benzodiazepines in the ICU is waning as questions about their safety and comparative efficacy begin to accumulate.

Oversedation is not a new observation in the ICU and is most commonly associated with continuous infusions of benzodiazepines. Prolonged and deep sedation, although necessary for some patients, has been associated with increased mortality at 6 months and significant morbidity, including prolonged ICU stays, prolonged duration of mechanical

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*The clinical practice guidelines for managing pain, agitation, and delirium in adult patients in the intensive care unit, the basis for this Point Counterpoint debate, were developed by the American College of Critical Care Medicine, which is the educational arm of the Society for Critical Care Medicine.

ventilation, and increased resource utilization, as well as delirium and psychologic morbidity, in ICU survivors.[2,3] The new guidelines recommend several strategies to minimize unnecessary exposure to sedatives and opioids (e.g., nurse-driven titration algorithms, analgesia-first sedation, lighter sedation targets, and daily interruptions in sedation), but these recommendations focus on the delivery of sedation and analgesia, not necessarily the agents that are used to achieve these effects.[2] The problem is that pharmacotherapeutic choices are scarce. Traditionally, the options for pain control with supportive evidence have been limited primarily to opioids, whereas the options for controlling agitation and anxiety have been limited to benzodiazepines and propofol. Opioids provide moderate sedation in addition to analgesia, but either they have active metabolites that can accumulate (e.g., morphine, hydromorphone) or they are extremely lipophilic (e.g., fentanyl). Benzodiazepines have active metabolites that accumulate (e.g., midazolam), longer-than-ideal durations of activity (e.g., lorazepam, diazepam), and no analgesic effect. Propofol, while shorter-acting, has dose-limiting hemodynamic and metabolic side effects. It can be very difficult to individualize care when the tools we have are so few and so flawed.

Dexmedetomidine has been available in the United States since 2002 and in Canada since 2009 for short-term sedation of patients who are undergoing mechanical ventilation. Like clonidine, it is an α2 agonist that provides sedation, anxiolysis, and analgesia via potentiation of opioids by decreasing norepinephrine-mediated sympathetic activity. It is delivered by continuous IV infusion and has a 15-min onset and a 3-h half-life in patients with normal liver function. Unlike opioids and benzodiazepines, it does not suppress the respiratory drive. Its major limitations are an inability to provide deep levels of sedation when these are required, the occurrence of dose-limiting bradycardia (particularly when administered as a bolus) and hypotension, and higher cost than the traditional pharmacotherapeutic options (about $400/day for a 70-kg patient, as compared with $25 to $35/day for midazolam or propofol).

A total of 27 randomized controlled trials ($n = 3056$ patients) have compared benzodiazepines with alternative agents for sedation in a variety of critically ill populations, with 24 of these trials using either propofol or dexmedetomidine as the comparator.[3] Twenty-four of these trials showed better outcomes with the non-benzodiazepine comparator (faster awakening, lower cost, earlier extubation or fewer days of ventilation,

shorter duration and lower incidence of delirium, less severe coma). Four large randomized controlled trials, with total enrolment of approximately 1500 patients, have compared dexmedetomidine with either propofol or benzodiazepines.[4-6] All of these trials have suggested that sedation with dexmedetomidine was associated with more coma-free and delirium-free days and that patients were more interactive and communicative with nurses. Whether dexmedetomidine is effective in treating delirium or if it is simply associated with less delirium relative to other deliriogenic drugs (e.g., benzodiazepines) is a current topic of debate. However, given the high prevalence of delirium in ICUs today, dexmedetomidine has a more favourable profile than benzodiazepines in this regard.[7,8]

Dexmedetomidine is a unique drug and is the only currently available medication that fits a niche within the therapeutic spectrum that no other drug fits at this time. By no means is it the ideal agent for treating agitation and analgesia in the ICU, but it is a necessary and welcome addition to the relatively bare cupboard of pharmacologic choices, particularly as we begin to recognize that lighter levels of sedation are warranted for many patients. The primary advantages of dexmedetomidine over currently available benzodiazepines and opioids are three: (1) patients sedated with dexmedetomidine are more easily arousable and interactive; (2) the lack of respiratory depression observed in dexmedetomidine sedation offers utility in the peri-extubation period; and (3) sympatholytic and antidelirium effects can be useful in patients with agitation or delirium, excluding those who are experiencing active drug withdrawal.[5,8-10] Dexmedetomidine should be considered for sedation and co-analgesia for ICU patients in whom light sedation and arousability are desired but the hemodynamic effects of propofol would be detrimental, as well as for patients with agitation or delirium in the peri-extubation period, to facilitate anxiolysis and cooperation without causing respiratory depression.

There is a role for dexmedetomidine in the management of ICU patients undergoing mechanical ventilation in Canada, but this drug cannot replace any of the drugs in current use. Deeper sedation is required for many critically ill patients, meaning there is still a role for benzodiazepines. Propofol is a reasonable alternative, but its hemodynamic and metabolic effects limit its utility for some patients. We need a greater selection of therapeutic options to address the broad range of patients' therapeutic needs. Dexmedetomidine, although imperfect, offers advantages over other agents, particularly benzodiazepines. The challenge for the clinician is balancing responsible drug usage with accountability for drug-related outcomes.

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THE "CON" SIDE

A hasty judgment is a first step to recantation.
—Publilius Syrus

Since publication of the first critical care guidelines for sedation, in 1995,[1] clinicians have been struggling with the optimal pharmacotherapeutic approach to sedation in the intensive care unit (ICU). The ideal sedative agent (and its dose) must address the complex and dynamic interplay of pain, anxiety, delirium, and general medical status, and must also meet patient-specific sedation goals, without causing excess adverse effects. No small task, indeed.

Dexmedetomidine is the first sedative agent to enter the Canadian market in over 10 years. Although it is not a new drug, dexmedetomidine's unique mechanism of action, the lack of associated respiratory depression, and its IV formulation have generated a flurry of published literature and much discussion in the ICU community. The recently updated sedation guidelines,[2] which appeared in *Critical Care Medicine*, suggest that dexmedetomidine, along with propofol, should be used preferentially over benzodiazepines in patients undergoing mechanical ventilation. We are concerned about the sweeping nature of this suggestion in such an influential publication. The literature is equivocal in its support of dexmedetomidine, which raises important questions about it being favoured over benzodiazepines.

Proponents of dexmedetomidine will point to 2 randomized trials that report lower prevalence of delirium[3] and shorter duration of mechanical ventilation[4] with this agent, relative to midazolam, the benzodiazepine most commonly used for sedation in the ICU. Notably, the incidence or prevalence of delirium was not a primary outcome in either of these studies. Only the smaller of the 2 studies (SEDCOM) showed significantly lower delirium prevalence and more delirium-free days, although, curiously, similar proportions of patients in each group needed haloperidol to treat delirium.[3] As a possible explanation, some have suggested that assessment of delirium may be confounded by the deeper sedation associated with benzodiazepines, which introduces a bias favouring dexmedetomidine.[5]

The second study showed a benefit of dexmedetomidine in one of its primary outcomes, the duration of mechanical ventilation.[4] However, this benefit did not translate into a shorter length of stay in the ICU or the hospital. Interestingly, in this study, dexmedetomidine was more than twice as likely as midazolam to be stopped because of lack of efficacy.

A third trial compared dexmedetomidine with lorazepam administered by continuous infusion.[6] Despite a higher aggregate incidence of coma-free and delirium-free days with dexmedetomidine, there was no decrease in delirium alone. The dexmedetomidine group used significantly more fentanyl and also more antipsychotics (although the latter was not statistically significant). These results support the observation by nurses in the study that over twice as many patients in the lorazepam group were oversedated. Given these puzzling findings and the infrequent use of lorazepam by continuous infusion in current practice, the clinical impact of this study is clearly limited.

While markers of "efficacy" have been inconsistent in the clinical trials published to date, dexmedetomidine has been uniformly associated with an increase in adverse effects, specifically bradycardia.[3,4,6] This outcome, of course, is of particular concern in the hemodynamically at-risk ICU population. In the largest of the trials comparing dexmedetomidine with midazolam, bradycardia was nearly 3 times as likely and hypotension twice as likely.[4]

Compared with its alternatives, dexmedetomidine has a narrower range of therapeutic uses and is therefore less desirable for many patients. Lack of anticonvulsant properties and inability to produce the deep sedation required for managing traumatic brain injury or ventilator asynchrony are 2 important limitations to its use. Furthermore, concerns about vasoconstrictive properties (cerebral and peripheral) have limited the use of dexmedetomidine in patients at risk of cerebral vasospasm and those undergoing microvascular procedures.[7] Despite the publication of several small studies, the safety of this agent has not been confirmed in these significant neurologic critical care populations.[8,9]

In the recently published SLEAP study,[10] which looked at the impact of protocolized sedation (using only opioids and benzodiazepines) and daily interruption of sedation in a mixed ICU population, the prevalence of delirium was just over 50% overall, considerably less than in the SEDCOM trial.[3] Although the SLEAP study showed no benefit of daily interruption of sedation, its results do raise the question of whether the focus should be on providing sedation in a protocolized fashion rather than on use of any specific agent. Strikingly, the results of a recent study examining the relationship between the drugs fentanyl and midazolam and resultant delirium and coma suggest that delirium may be related to inflammatory status and *not* to midazolam.[11]

Finally, cost must be brought into the dicussion, given that dexmedetomidine is approximately 10 times more expensive than generic midazolam. Cost-minimization data from the SEDCOM study have suggested that, despite the higher acquisition cost, the use of dexmedetomidine over midazolam results in significant cost savings associated with ICU stay and mechanical ventilation.[3,12] However, bias introduced by manufacturer sponsorship, lack of a significant difference in ICU length of stay, lack of protocolized weaning of sedation, and censoring of patient data for one-third of the patients, for whom the study drug was discontinued before extubation, undermine the validity of the conclusions. Some investigators, in fact, have argued that reducing the duration of mechanical ventilation does not translate into cost savings because of the high fixed costs associated with an ICU stay.[13] More robust pharmacoeconomic data will be needed to justify the excess cost of dexmedetomidine over, in this case, midazolam.

Benzodiazepines, although not perfect, are well understood, safe, and inexpensive. Until compelling data show that dexmedetomidine provides a clear therapeutic benefit worth the excess cost, these agents should not be abandoned. Over the past 15 years, the critical care community has witnessed the introduction of several therapies that have been ushered in with early positive trials and much fanfare, only to be subsequently disappointed by further trial data; activated protein C, low-dose glucocorticoids, and intensive glucose control in sepsis are

examples. In our enthusiasm, we have likely hurt some of the very patients we seek to help by lowering the bar on the quality and quantity of evidence we demand to shift our practice. Undoubtedly, the current pharmacologic armamentarium for sedation is imperfect, and improvement in how sedation is delivered to critically ill patients is a laudable goal. However, if we are honest about the evidence to date, dexmedetomidine is clearly not our silver bullet. We would be remiss in jumping hastily to the conclusion that dexmedetomidine should be given preference over benzodiazepine as an ICU sedative.

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ON THE FRONT COVER

Stawamus Chief
Squamish, British Columbia.

This photo was taken on July 20, 2013, from the top of the first peak of Stawamus Chief (or simply "The Chief") in Squamish, British Columbia. The Chief is a granite dome located about 60 minutes' drive north of Vancouver.

The photo was taken with a Canon Rebel T1i by Gary Peng, currently a pharmacy resident with Lower Mainland Pharmacy Services. After a long hike with fellow residents and some waiting, the clouds finally cleared to reveal the view captured in this image.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to Colleen Drake at cdrake@cshp.ca.