Commentary

Narcotic-based sedation regimens for critically ill mechanically ventilated patients

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Abstract

Sedatives and analgesics are routinely used in the intensive care unit to relieve pain and anxiety. These agents have numerous side effects and may contribute to poor outcomes such as increased length of mechanical ventilation, longer ICU stays and acute and long-term cognitive dysfunction. Modifying sedation paradigms utilizing either narcotic-based regimens with remifentanil or fentanyl, or by using α_2 agonists such as dexmedetomidine may help in improving these outcomes in critically ill patients.

Benzodiazepines and narcotics are an integral component of the pharmacological treatment of millions of critically ill mechanically ventilated patients. This month in *Critical Care*, Breen and coworkers [1] report that narcotic-based sedation strategies, compared with the traditional approach involving benzodiazepines with supplemental analgesics for pain, might have improved patient outcomes. In this prospective, randomized, unblinded trial, target-based sedation with remifentanil and rescue midazolam was associated with decreased duration of mechanical ventilation and shorter times to extubation compared with sedation with benzodiazepines, with rescue fentanyl or morphine. The study has important ramifications in the light of recent investigations that have questioned whether currently used strategies for providing sedation and analgesia in mechanically ventilated patients are optimal.

The Society of Critical Care Medicine, in its 2002 clinical practice guidelines [2], recommended protocolized target-based sedation. Those guidelines recommend the use of lorazepam for long-term sedation and midazolam or propofol for short-term sedation, with fentanyl or morphine for analgesia. Unfortunately, benzodiazepines have numerous adverse effects, including the potential for prolonged ventilation, development of delirium and contribution to chronic cognitive dysfunction [3-7]. Hence, modification to delivery patterns of sedatives or changing sedation paradigms could alter patient outcomes.

Prior studies [6,8-10] have demonstrated reductions in duration of mechanical ventilation and intensive care unit (ICU) length of stay with protocolized, target-based sedation and daily wake-up trials, and by modifying the route of administration of these drugs (intermittent versus continuous infusion). Although sedatives and analgesics act on the central nervous system, studies comparing sedative and analgesic regimens have tended not to report neurological outcomes. This was not possible until recently because of the lack of monitoring tools that could measure outcomes such as delirium in nonverbal patients. Newer reliable and validated sedation scales such as the Sedation Agitation Scale, Richmond Agitation Sedation Scale, and the Confusion Assessment Method in the ICU for detecting delirium in mechanical ventilated patients permit measurement of these outcomes [11-14]. This is important because delirium is an independent predictor of prolonged mechanical ventilation, longer ICU stay and mortality [15].

Benzodiazepines and propofol act primarily as γ-aminobutyric acid (GABA) agonists to exert their sedative effects. Along similar lines, alcohol is an agonist at the GABA receptor, which is believed to be the probable mechanism underlying the cognitive impairment seen in alcoholic persons [16,17]. Use of novel agents that are GABA receptor sparing (e.g. remifentanil at the μ opioid receptor or dexmedetomidine at the α_2 receptors) may help to reduce exposure to benzodiazepines and consequently the degree of brain dysfunction, and may improve outcomes such as duration of mechanical ventilation and ICU length of stay.

GABA = γ-aminobutyric acid; ICU = intensive care unit.

Remifentanil has been shown to be efficacious and safe in critically ill patients [18]. It is an attractive agent for sedation in the ICU because of its favorable pharmacokinetic and pharmacodynamic profiles. The drug is metabolized by non-specific plasma esterases and is therefore independent of the function of organs such as the liver and kidneys. Studies in critically ill patients [19,20] have demonstrated a predictable and constant offset time, with little or no accumulation of drug over time. However, there are conflicting reports on the development of tolerance as well as withdrawal after discontinuation of remifentanil [20-22]. Additionally, remifentanil does not possess amnestic or anxiolytic properties.

The study reported in the present issue by Breen and coworkers [1] was an unblinded study conducted in 10 countries and in 15 medical centers. Although the titration of remifentanil was based on a fixed protocol, titration of the comparator benzodiazepine infusion was left to the discretion of the individual centers, based on local clinical practice. Furthermore, even though there was no statistical difference in the time from start of study drug to the beginning of the weaning process, this process was begun in the remifentanil group an average of 15 hours earlier. In addition, it is not clear why the patients in the comparator benzodiazepine arm took longer to be extubated once weaning was instituted. It would be interesting to know whether the benzodiazepine group took much longer to return to an acceptable level of arousal for extubation or whether there were other confounding factors, such as delirium, that delayed extubation in this group. The authors do mention that the sedation levels were matched in both groups, during treatment and in the post-treatment period, and that the differences were due to the drug *per se* and not the level of sedation. However, a physiological basis for this difference is not offered. This is important in the context of an unblinded trial, in which there is always the potential for bias.

What this field now needs is a new guard of studies focusing on acute and long-term cognitive outcomes of sedative regimens in addition to outcomes such as days on mechanical ventilation and ICU length of stay. Modifying sedation paradigms by utilizing agents such as remifentanil or dexmedetomidine may provide clinicians with alternatives to the 'gold standard' benzodiazepines. However, for that to happen we need rigorously conducted, blinded, randomized controlled trials.

Competing interests

The author(s) declare that they have no competing interests.

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