Toward Tailored Sedation with Halogenated Anesthetics in the Intensive Care Unit?

S UBSTANTIAL efforts have been made over the past decade to focus more attention on sedation and analgesia management in critically ill patients. Although evidence is accumulating of painful and unpleasant experiences suffered during length of stay in the intensive care unit (ICU) that can affect quality of life, even after discharge, more is also known about the impact of excessive use of sedatives (hypnotic drugs) on patient outcome. Indeed, intravenous hypnotics have been linked to prolonged duration of mechanical ventilation, increased length of ICU stay, increased delirium and altered mental status, ventilator-associated pneumonia, self-extubation, and drug withdrawal syndrome. Thus, ICU physicians face an awkward dilemma in their search for maximal comfort for their patients: to relieve pain and agitation and facilitate mechanical ventilation with unrestricted use of analgesics and sedatives, or to limit sedation and its side effects. In this issue of ANESTHESIOLOGY, Sackey et al. illustrate this dilemma in a case scenario where a 24-h conventional protocol of deep sedation with midazolam, propofol, morphine, and atracurium after major tracheal surgery was followed over the next 24 h by the combined use of isoflurane and clonidine to permit rapid ventilator weaning and shorter wake-up time. The authors advocate that such a tailored sedation and analgesia plan based on each individual’s characteristics should represent the future gold standard in sedation management. They also promote the implementation of halogenated agents in the ICU based on favorable reports of the anesthesia-trained ICU physicians in Sweden as well as on the advantageous short-term elimination of these drugs. This case scenario gives us the opportunity to discuss two major issues: (1) How to optimize sedation and analgesia in the ICU, and (2) what is the place of halogenated agents in the arsenal of ICU sedative agents.

Any approach to optimizing sedation and analgesia in the ICU should first consider defining the levels of sedation and analgesia at which the patient should be maintained. Certain patient populations require a deep state of sedation (e.g., those with increased intracranial pressure or with acute respiratory distress syndrome). The use of continuous infusions of sedatives and a neuromuscular blocking agent to keep the patient immobile for several hours after a surgical procedure, which compromises the airway patency, is understandable in the case report presented. The subsequent change in sedative drugs is actually not uncommon because most ICU patients require a change in drug dose or even in the sedation and analgesia strategy during their stay in ICU. However, regardless of the level of pain and sedation deemed as optimum, the paramount point is the ability to assess the pain and sedation in order to adjust drug requirements accordingly or even to justify drug replacement. Only then could a “tailored sedation and analgesia to individual needs” be achieved. Measurements of pain, sedation (vigilance), and delirium can be made with the use of numerous validated and reliable clinical instruments and, occasionally, with the bispectral index in paralyzed patients. Although sedation and pain assessment rates remain below 40% in mechanically ventilated patients, we recently demonstrated an association between pain assessment and reduced number of ventilator days and length of ICU stay; this effect was possibly related to concomitant higher rates of sedation assessment and a reduction in sedative drug dose when pain was assessed. An association was also found between the systematical evaluation of pain and agitation levels and shorter mechanical ventilation duration.

Another point to consider in sedation and pain management is the integration of these measurements in standard protocols and sedation strategies. There is large evidence that the administration of sedatives and analgesics, according to these principles, can markedly reduce the duration of mechanical ventilation and the incidence of sedation-related side effects: protocol-directed sedation according to consciousness levels, daily interruption of sedation, combined

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sedation and ventilator weaning protocol, and spontaneous breathing trial during ventilatory support. Common to all of these strategies is the repeated measurement of level of consciousness, and possibly pain, to achieve the desired goal. In the current case scenario, the drug replacement with clonidine and isoflurane was planned to accelerate sedative and ventilator weaning, although there was no reported evidence of sedation-related side effects in this patient (i.e., agitation, excessive doses of sedatives, or drug withdrawal syndrome). Therefore, one is left to wonder whether stopping conventional sedation could have been attempted with no subsequent drug replacement.

The second point raised by this case scenario is the place for halogenated agents as an alternative in the arsenal of ICU sedative agents. This opportunity is available for exploitation in Europe. Isoflurane and sevoflurane can be administrated to ICU patients through a judicious delivery method, regardless of the ICU ventilator, pending a continuous gas monitoring, and exhaled with a simple scavenging device. Considering the huge amount of experience accumulated over decades with the use of halogenated agents in the operating room and their pharmacological profile permitting a rapid emergence once delivery has been stopped, it has been tempting to import this alternative into the ICU. Although the authors are leaders in their field to promote this method in sedation, I would temper their enthusiasm for certain reasons. First, there remains a paucity of data regarding the efficacy and safety of such a sedative method in ICU patients. Most clinical studies have explored the feasibility and efficacy of halogenated agents for use in short-term sedation (i.e., less than 96 h) and in a relatively small number of postoperative patients. Because there remain uncertainties about the toxicity of the degradation products (e.g., fluoride), the long-term administration of isoflurane and sevoflurane is largely unknown. The current authorization criteria allow for the prolonged use of halogenated agents only on an off-label basis at the physician’s discretion. In addition, no randomized controlled trial has yet been conducted in critically ill patients (i.e., patients with one or more organ failure and comorbidities) to compare inhaled anesthetic agents and intravenous sedatives. Finally, it should be noted that halogenated agents have been associated with several side effects (e.g., arrhythmias, hepatotoxicity, and neurotoxicity) and are contraindicated in patients with increased intracranial pressure. In the current case scenario, isoflurane was used for a few hours in the hope of facilitating recovery. The resort to the use of halogenated agents as sedatives in the ICU could represent an opportunity to investigate, for example, if the patient shows dangerous signs of agitation at the cessation of properly conducted intravenous sedation or signs of inadequate levels of sedation despite large sedative doses.

In conclusion, no prominence of one drug or one strategy has been found in the management of sedation and analgesia in critically ill patients that incorporates the repeated measurement of levels of vigilance and pain to permit the titration and adjustment of drug doses accordingly. Considering the large proportion of patients still kept in a deep state of sedation, studies are warranted to reassess the systematic use of hypnotics (not analgesics) in terms of risk/benefit ratio, as recently suggested. At first, it is time to recommend the massive use of instruments for measuring sedation, pain, and delirium that would assist healthcare providers in the optimum use of sedatives and analgesics in the ICU. This may improve patient long-term outcome.

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