Extending the Use of Inhaled Anesthetics Beyond the Operating Room: a Giant Snake Creeping Into the Intensive Care Unit

Sedation for critically ill patients has been provided for decades, and yet the types of sedatives and effects and consequences of sedation have been largely unexplored. Recently, new drugs and devices for intensive-care-unit (ICU) sedation have been introduced in the market, ranging from a selective α_2-adrenergic receptor agonist, dexmedetomidine,[1] which provides sedation without causing respiratory depression and the patient remains wakeable, to inhaled anesthetics that allow sedation to a wide range of depths, from light sedation to a depth of general anesthesia, via the "anesthetic conserving device" (brand name AnaConDa).[2]

The concept of sedation in the critical-care setting has evolved over the past 20 years, from the goal of inducing deep sedation (in which the patient is unaware of his or her surroundings) to the modern goal of keeping the patient awake and cooperative, or to a specified sedation goal, based on the given institution's sedation protocol.[3-6] Daily temporary discontinuation of sedatives reduces the duration of mechanical ventilation and ICU stay.[7,8] Considering the emerging data, several questions still need answers. What types of sedation are ideal? What are the sedation targets for different patient populations? What are the short-term and long-terms effects and consequences of sedation?

Does One Size Fit All?

In this issue of RESPIRATORY CARE, L'Her and colleagues report a study in which they explored an alternative modality to the classic administration of intravenous ICU sedation.[9] For decades, volatile agents have been used in the operating room as short-term intraoperative anesthetics. Recently, new devices were approved in Europe for delivery of inhaled anesthetics in the ICU. These devices allow recycling of gas, which minimizes air pollution. L'Her and colleagues, in their observational study of 15 patients,[9] found that isoflurane could be safely administered for a relatively long period (up to 15 d) and allowed for rapid awakening and hemodynamic stability at the doses used. No hepatic or renal adverse effects were found, which confirms other researchers' findings.[2,10] L'Her et al also suggest that the cost of isoflurane sedation is less than that of benzodiazepine sedation. These features seem ideal for ICU sedation.

The interpretation of these findings needs to account for several limitations of the study design and the sedation practices at L'Her's institution. The patients received a relatively high concentration of isoflurane (end-tidal concentration $\leq$ 1%, median value range 0.5–1.0%), and sedation was adjusted to achieve a Ramsay score of approximately 5 (range 2–6), at least in the acute phase of the critical illness. That sedation-depth range may not be generalizable to sedation used in other ICUs. Furthermore, despite targeting heavy sedation goals, isoflurane administration resulted in over-sedation after 24 hours in 6 of 15 patients. Although the risk of over-sedation is a concern, if high doses of isoflurane were used to achieve relatively deep sedation, the data suggest that a lower concentration might prove acceptable from a safety standpoint. However, importantly, this case series did not have a comparison group, so we must use caution regarding the inference about efficacy and safety. With these caveats, these data will definitely stimulate interest in the critical care community. Nevertheless, a difficult road lies ahead for the widespread use of inhaled anesthetics in critical care medicine. Will non-anesthesiology-trained intensivists and critical care nurses feel comfortable with providing inhaled anesthetics? Do established ICU privileges grant permission for clinicians not specifically trained in the use of anesthetics to deliver inhaled anesthetics? Are there sufficient data to demonstrate safety? Have concerns about excessive agent consumption and environmental contamination been adequately addressed? Are there sufficient efficacy data on inhaled anesthetics for ICU sedation? The answer to most of these questions is "not quite."

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The AnaConDa device should allow efficient conservation of the volatile agent and thus minimize or even eliminate environmental contamination and substantially reduce agent consumption, compared to traditional vaporizers.[11] Despite the availability of preliminary environmental data, little is known about the safety of this delivery device in the ICU environment, especially as it relates to long-term, low-level exposure of health care professionals, and to hazards related to spillage. Spillage can be minimized by rigorously standardizing the syringe-replacement procedures. Besides spillage, a bench study with a closed-circuit anesthesia machine found that refilling transiently changed the concentration of gas delivered. It also showed that a standard Luer-Lok made it possible to connect the halogenate syringe to an intravenous infusion line.[12] A medical device alert was issued in 2006 by the United Kingdom's Medicine and Healthcare Products Regulatory Agency, related to an adverse incident of anesthetic overdose that occurred during the use of an AnaConDa, so the manufacturer changed the device's instructions and eliminated the Luer-Lok connection between the syringe and the AnaConDa device. Other technical problems that have been described include a case of occlusion of the evaporator rod by respiratory secretions.[2]

Remarkable changes in the expired volatile agent can occur with changes in ventilator settings, particularly with increase in tidal volume or reduction of fresh gas flow.[12] Whereas the device is simple to use, ICU nursing staff might have limited knowledge of the pharmacokinetics and pharmacodynamics of volatile agents.

However, it is likely that if the safety of the administration of inhaled anesthetics is confirmed, there could be a potentially important role of this administration route in the ICU. The fact that isoflurane could be administrated for a relatively long period of time could be a very attractive feature for patients who require high-dose propofol for protracted sedation, and for pediatric patients at higher risk of propofol-infusion syndrome.[13] The ability of rapid awakening mimics, for example, the favorable pharmacokinetics properties of propofol. The added benefit of maintaining hemodynamic stability can also benefit most critically ill patients. However, sedation-induced blunting of the sympathetic response at higher alveolar concentrations than those used in the study by L'Her et al might be associated with unanticipated hypotension. A previous study of ICU sedation observed a blood pressure decline after 2 hours of the inhaled anesthetic, compared with intravenous midazolam.[10]

Recent literature suggests that reducing the amount of sedation by daily discontinuation of sedative reduces the duration of mechanical ventilation and ICU stay, and may even improve mortality.[7,8] Daily sedative interruption is possible with volatile agents. Preliminary data on isoflurane versus midazolam for 24–96 hours indicate more rapid awakening with isoflurane.[2,10] Attractive characteristics of isoflurane and its short duration of action make it potentially easy to manipulate to achieve a predetermined sedation goal.[10] Its potent bronchodilation properties could be advantageous in certain clinical situations, and in the experimental setting isoflurane demonstrated anti-inflammatory properties.

The interest in inhaled anesthetics could also expand to as yet less-explored properties, including modulation of reperfusion injury and sepsis-induced inflammation. Recent experimental data suggest that isoflurane has systemic and pulmonary anti-inflammatory and preconditioning properties. Isoflurane pretreatment protects the vasculature during lipopolysaccharide-induced inflammation[14] and attenuates inflammation via direct anti-inflammatory and anti-necrotic (attenuation of apoptosis) effects during renal[15,16] and lung[17] ischemia-reperfusion injury. The ability to administer inhaled anesthetics to ICU patients might provide a new opportunity to explore unknown benefits of inhaled anesthetics in patients with acute lung injury.

Another consideration concerning prolonged exposure is the need to account for the potential association of inhaled anesthetics and cognitive decline associated with an increase in amyloidogenesis and plaque deposition in the brain, which has been implicated in Alzheimer disease.[18] A possible molecular explanation for neurocognitive dysfunction following inhaled anesthesia was supported by in vitro and in vivo studies that demonstrated increased aggregation of amyloid β in predisposed animals.[19-21] Isoflurane might also cause cognitive decline through mechanisms other than plaque deposition.

Further comparative studies are needed to provide controlled evaluation of the safety and efficacy of inhaled anesthesia for ICU sedation and to allow the interpretation of these data from a wider perspective. It is likely that one or more of these studies need to be conducted prior to the acquisition and use of the delivery device, along with the end-tidal volatile anesthetic agent monitoring by critical care units. Additionally, studies to compare inhaled anesthetics to other ICU sedatives (eg, benzodiazepines and propofol) need to be undertaken. Finally, it remains unclear if prolonged sedation protects from or causes adverse mental-health effects, or whether it affects the development of delirium or adverse psychiatric outcomes, including post-traumatic stress disorder, delusional memories, anxiety, or depression. Preliminary data suggest benefit from isoflurane (compared to midazolam) sedation on delusional memories and hallucinations.[22] The effects of different sedatives and sedation depths on these outcomes remain largely unknown.

In summary, inhaled anesthetics do possess attractive features for ICU sedation and deserve further study. However, the research agenda should include a number of safety issues that need to be addressed before wider use should be considered. Given the current state of knowledge, if inhaled anesthetics are used for ICU sedation, expiratory gas monitoring and scavenging should be used.

Miriam M Treggiari MD PhD MPH
Department of Anesthesiology and Neurological Surgery
Harborview Anesthesiology Research Center
University of Washington School of Medicine
Seattle, Washington

REFERENCES

1. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298(22):2644-2653.
2. Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med 2004;32(11):2241-2246.
3. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27(12):2609-2615.
4. Brattebo G, Hofoss D, Flaatten H, Muri AK, Gjerde S, Plsek PE. Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. BMJ 2002;324(7350):1386-1389.
5. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Crit Care Med 2008;36(2):427-433.
6. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. Crit Care Med 2008;36(5):1444-1450.
7. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. New Engl J Med 2000;342(20):1471-1477.
8. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371(9607):126-134.
9. L'Her E, Dy L, Pili R, Prat G, Tonnelier JM, Lefreve M, et al. Feasibility and potential cost/benefit of routine isoflurane sedation using an anesthetic-conserving device: a prospective observational study. Respir Care 2008;53(10):1295-1303.
10. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. BMJ 1989;298(6683):1277-1280.
11. Sackey PV, Martling CR, Nise G, Radell PJ. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. Crit Care Med 2005;33(3):585-590.
12. Berton J, Sargentini C, Nguyen JL, Belii A, Beydon L. AnaConDa reflection filter: bench and patient evaluation of safety and volatile anesthetic conservation. Anesth Analg 2007;104(1):130-134.
13. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered by the AnaConDa. Paediatr Anaesth 2005;15(10):879-885.
14. Plachinta RV, Hayes JK, Cerilli LA, Rich GF. Isoflurane pretreatment inhibits lipopolysaccharide-induced inflammation in rats. Anesthesiology 2003;98(1):89-95.
15. Lee HT, Kim M, Kim M, Kim N, Billings FT, D'Agati VD, et al. Isoflurane protects against renal ischemia and reperfusion injury and modulates leukocyte infiltration in mice. Am J Physiol 2007;293(3):F713-F722.
16. Lee HT, Emala CW, Joo JD, Kim M. Isoflurane improves survival and protects against renal and hepatic injury in murine septic peritonitis. Shock 2007;27(4):373-379.
17. Liu R, Ishibe Y, Ueda M, Hang Y. Isoflurane administration before ischemia and during reperfusion attenuates ischemia/reperfusion-induced injury of isolated rabbit lungs. Anesth Analg 1999;89(3):561-565.
18. Kuehn BM. Anesthesia-Alzheimer disease link probed. JAMA 2007;297(16):1760.
19. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology 2004;101(3):703-709.
20. Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, et al. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. Neurobiol Aging 2008;29(7):1002-1010. doi:10.1016/j.physletb. 2003.10.071.
21. Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, et al. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. J Neurosci 2007;27(6):1247-1254.
22. Sackey PV, Martling CR, Carlsward C, Sundin O, Radell PJ. Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam--a pilot study. Crit Care Med 2008;36(3):801-806.

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Correspondence: Miriam M Treggiari MD PhD MPH, Department of Anesthesiology, Harborview Anesthesiology Research Center, Harborview Medical Center, Box 359724, 325 Ninth Avenue, Seattle WA 98104. E-mail: treggmm@u.washington.edu.