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Case Scenario: Tailored Sedation to the Individual Needs of the Intensive Care Unit Patient

Peter V. Sackey, M.D., Ph.D.,* Lars I. Eriksson, M.D., Ph.D.,† Claes-Roland Martling, M.D., Ph.D.,‡ Peter J. Radell, M.D., Ph.D.§

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THE many challenges of modern multidisciplinary critical care require wakeful attention from those caring for critically ill patients. Increasingly sophisticated technology, as well as a deeper understanding of pathophysiology, challenges intensive care unit (ICU) physicians in a myriad of ways. The following case report exemplifies the use of overlapping disciplines to meet the challenge of promptly waking up a patient after 2 days of deep sedation in the ICU. The purpose of this case scenario is to highlight the value of planning tailored sedation for the individual ICU patient and situation.

* Postdoctoral Fellow, † Professor, ‡ Associate Professor, Department of Anesthesiology, Surgical Services and Intensive Care Medicine, Karolinska University Hospital, Stockholm, Sweden. § Associate Professor, Department of Pediatric Anesthesia and Intensive Care, Karolinska University Hospital.

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Address correspondence to Dr. Radell: Department of Physiology and Pharmacology, Section for Anesthesiology and Intensive Care Medicine, Karolinska Institutet, Stockholm, Sweden. peter.radell@karolinska.se.

Case Report

A 22-yr-old woman diagnosed with papillary thyroid cancer was scheduled for thyroid surgery. The tumor penetrated the tracheal wall, necessitating extensive surgery, including the likely removal of several involved tracheal rings. The patient was preoperatively informed about the planned surgery and the likelihood of delayed extubation in the intensive care unit, as well as the need for restricted neck movements in the days after extubation.

To achieve as radical a resection of the tumor as possible, four tracheal rings were removed, and the left recurrent laryngeal nerve was sacrificed and anastomosed after removal of the tumor. As a result of anticipated postsurgical tension to the anterior part of the neck after primary suturing of the trachea, the surgical team requested that the patient remain intubated with her neck flexed for the first 36 postoperative h.

The patient was transferred intubated to the general ICU. She was kept sedated with propofol 5 $mg \cdot kg^{-1} \cdot h^{-1}$, midazolam 5 mg/h, and morphine 6 mg/h for the first night. Atracrium was started at 10 mg/h, with intermittent train-of-four monitoring, on the first postoperative evening to ensure complete immobility. To maintain a train-of-four rate of two twitches or less, the infusion of atracurium was increased to 20 mg/h. At the surgeon's request, nimodipine 5 mg/h was also started for the purpose of stimulating nerve regeneration after the nerve anastomosis. Noradrenaline was required at an initial rate of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to maintain a mean arterial pressure above 65 mmHg.

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What Are the Goals of Sedation in ICU Patients?

Patient comfort and safety are two important priorities of sedative and analgesic treatment in critically ill patients.[1] Pain and anxiety are reported by many patients after an ICU stay.[2] Pain and anxiety lead to increased central nervous sympathetic output, potentially resulting in cardiovascular problems, such as hypertension and tachycardia. Central respiratory activation leads to tachypnea and ventilator dyssynchrony, which may lead to hypoxia and hypercarbia in the mechanically ventilated critically ill patient. In addition, memories of pain, anxiety, and other negative feelings from the ICU may be associated with increased risk of posttraumatic stress disorder symptoms.[3]

Patient comfort implies that the ICU patient not experience severe pain, anxiety, or other adverse feelings. In cases where the patient cannot be made reasonably comfortable with analgesia and reassuring information, sedation may be needed.[1] In some patients, this need may arise during mechanical ventilation or during procedures and, at times, be accompanied by the use of neuromuscular blocking agents (NMBA).[4,5]

Patient safety relates in part to actions that jeopardize ongoing ICU treatment or to the risks of self-injury, inadvertent self-extubation, or catheter removal. Sedative treatment may be necessary to minimize the risk of such events or to facilitate adequate ventilation and oxygenation during mechanical ventilation.[1]

When treating patients with sedatives and analgesics to meet these goals, one challenge is to avoid oversedation because this may lead to well-recognized clinical problems, such as cardiorespiratory depression, with hypotension and bradycardia, or inadequate spontaneous ventilation and prolonged ventilator treatment.[1]

What Drugs Are Used for Sedation and Analgesia in Mechanically Ventilated ICU Patients?

The drugs most commonly used for sedation during mechanical ventilation in ICU patients are either benzodiazepines (midazolam or lorazepam) or propofol, commonly combined with an opiate infusion for analgesia.[4–7] Midazolam is a short-acting benzodiazepine, frequently used for long-term sedation in intubated ICU patients. Lorazepam has slightly slower onset of effect and longer half-life and is commonly used in the United States for sedation during mechanical ventilation but rarely used in Europe.[6] Both drugs act *via* enhancement of GABA-ergic transmission and produce a state of anxiolysis and amnesia. Propofol is also commonly used for sedation and has the benefit of relatively short duration of action. Haloperidol is usually used as an empirical treatment for agitation, delirium, and hallucinations in ICU patients but rarely used alone for sedation.[1] Barbiturate infusions are primarily used in patients with increased intracranial pressure, but because of accumulation in fatty tissue, they are rarely used solely for sedative purposes. The α_2-agonists clonidine and dexmedetomidine appear to be used increasingly for sedation alone or in combination with other sedatives.[7–9]

Continued Management of the Patient

Because uncontrolled movements were considered to pose a risk for potential surgical complications, it was planned—for patient safety reasons—that the patient remain intubated and immobilized for 36 h postoperatively. Furthermore, reintubation after uncontrolled self-extubation could be technically difficult because of possible edema or hematoma after the tracheal surgery. The NMBA was administered for patient safety reasons, whereas sedation and analgesia were given primarily for patient comfort/amnesia. With NMBA administration, the initially prescribed deep sedation target (Motor Activitity Assessment Scale[10] 0) could not be monitored, leading to high sedative doses to minimize the risk of awareness. At emergence from the drug-induced coma and muscle paralysis, it was vital that the patient regain full consciousness and muscle tone to maintain airway patency, particularly with regard to a likely left laryngeal recurrence paresis. Furthermore, it was important to minimize the risk of agitation and disorientation so the patient would cooperate at an early stage and not risk the surgical outcome by uncontrolled head movements.

With these goals in mind, discussion in the ICU continued as to how to best manage the patient's sedation. On postoperative day 1, it was clear that the ongoing therapy, although allowing deep sedation and immobilization, would probably not result in a prompt return to full wakefulness and cooperation, a goal needed to be achieved for successful extubation and spontaneous breathing without jeopardizing the surgical repair. Although this case was somewhat exceptional, situations are not rare where deep sedation is combined with the need for quick conversion to clear wakefulness, particularly in cases with postoperative airway concerns. Other alternatives might include drugs with rapid metabolism and offset (*e.g.*, propofol combined with remifentanil). Our experience is that no therapy provides as quick a transition from deep sedation to wake-up as inhaled sedation. Thus, we decided to convert the administration of intravenous sedatives and NMBA to inhaled sedation with isoflurane. In addition, the sedation plan included the use of intravenous clonidine as a sedative adjunct if necessary at extubation. Although overt withdrawal symptoms were not anticipated, considering the relatively brief duration of sedation, there was concern that even a brief period of confusion or agitation during wake-up might risk the success of the surgical repair in this patient.

Isoflurane was delivered with the aid of the anesthetic conserving device (AnaConDa®; Sedana Medical AB, Stockholm, Sweden), initially at an infusion rate of 8 ml/h, with an end-tidal concentration target of 1.2%. Midazolam, propofol, and atracurium were tapered during the next 3 h before discontinuation, and morphine infusion was reduced to an hourly rate of 3 mg/h. During the period of parallel intravenous and inhaled sedation, noradrenaline infusion rate was 0.11 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but could be reduced to 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ within hours. The next morning, 36 h postoperatively, the surgeons and the ICU team decided to inspect

the airway fiberoptically and possibly extubate the patient. For this purpose, the patient was taken to the operating room. After concluding that there was no swelling or hematoma posing a risk to extubation, the definitive decision to extubate the patient was taken. Within minutes of terminated sedation, the patient showed signs of emerging. Extubation was successful, with the patient breathing spontaneously before extubation and with adequate oxygenation and ventilation. She was noted to be somewhat restless and tachycardic and was therefore given an intravenous clonidine bolus of 75 + 75 μg at the time of extubation. After returning from the operating room, additional clonidine 75 + 150 + 75 μg was given to calm the patient. Morphine boluses and a morphine infusion of 1 mg/h were administered. Glycopyrrolate was given to reduce secretions. With this strategy, the patient remained lucid and cooperative in the hours after terminated sedation. She received paracetamol and morphine for postoperative pain and was discharged uneventfully to the surgical ward the next day.

What Was the Rationale for Changing the Patient's Sedation to Isoflurane and Clonidine?

Recent clinical data indicate that sedation of ICU patients with benzodiazepines may contribute to confusion or overt delirium at termination of treatment.[11,12] In one study, the cumulative dose of lorazepam during the final 24 h of sedation was found to be an independent risk factor for the development of delirium.[11] Another study compared awakening from midazolam and propofol. In the treatment group, midazolam was replaced with propofol when extubation was anticipated within 24 h. In patients emerging from solely midazolam sedation, dangerous agitation (Sedation-Agitation Scale + 2) was more frequent than in those emerging from propofol sedation (54% *vs.* 8%).[12] In critically ill patients, midazolam infusions may lead to long and unpredictable wake-up times.[13,14] In patients with renal or hepatic failure, this is most evident, probably because of impaired metabolism and elimination and the accumulation of active metabolites.[13,14] High doses of propofol are believed to increase the risk of propofol infusion syndrome and are not recommended.[15] Prolonged use of NMBAs in ICU patients is a well-described risk factor behind the development of prolonged neuromuscular block and muscle paralysis.[16] Such side effects are more likely to occur when NMBAs with active metabolites are used and may not be possible to reverse with standard doses of anticholinesterase compounds.

The use of inhaled anesthetic agents for ICU sedation has been described in numerous case reports for the treatment of status asthmaticus, status epilepticus, or in patients difficult to sedate.[17–19] Prospective studies of inhaled anesthetic agents for critically ill or postoperative patients have shown good sedation efficacy at 0.2–0.5 minimum alveolar concentration and short, predictable wake-up times.[13,19–22] Desflurane sedation for delayed extubation after general surgery led to significantly shorter time to cooperation and time to extubation than propofol.[21] In another study comparing propofol with sevoflurane after cardiac surgery, time to extubation and time to cooperation were shorter for sevoflurane-sedated patients than for propofol-sedated patients.[22] The short time to awakening and cooperation with inhaled anesthetic agents compared with intravenous drugs, despite deep sedation,[13] are probably related to a route of elimination independent of renal or hepatic function, which are frequently impaired in critically ill patients. Inhaled sedation with isoflurane appears to promote early cooperation[13] and possibly contributes to less unreal or hallucinatory memories than midazolam sedation.[23] Such memories have been associated with the development of posttraumatic stress disorder symptoms.[24]

The α_2-agonist clonidine has been used in patients with alcohol withdrawal in the ICU[25] and as an adjunct to adult and pediatric sedation.[26,27] Generally, α_2-agonists have little effect on respiratory drive[28] but may have indirect circulatory effects, such as reduced blood pressure and heart rate as a result of central inhibition of sympathetic output.[29] In clinical practice, clonidine, as the sole sedative during mechanical ventilation, is often not sufficient. Likewise, dexmedetomidine appears to be valuable for sedation but may not be sufficient alone to achieve deep sedation. In a recent study, normal sedation targets were achieved with dexmedetomidine to the same extent as midazolam or propofol, but dexmedetomidine was inferior with regard to maintaining a deep sedation target (Richmond Agitation-Sedation Score of 4 or less).[30] The authors concluded that the use of dexmedetomidine was "not suitable as the sole agent for deep sedation."[30]

Recently, α_2-agonists have been demonstrated to reduce withdrawal symptoms at termination of conventional sedation. In one study, clonidine was used to attenuate the behavioral and autonomic stress response, after termination of propofol-remifentanil sedation, and to facilitate extubation.[9] In this observational study, 25 of 30 patients responded to bolus doses of clonidine, in that their increased heart rate, blood pressure, and oxygen consumption returned to values similar to those before terminating sedation. Doses were higher than usually prescribed (900 μg and repeated if needed). In a study by Reade *et al.*, dexmedetomidine was compared with haloperidol for treating patients deemed otherwise ready for extubation but where agitated delirium precluded extubation.[31] Dexmedetomidine patients were extubated significantly faster than those receiving haloperidol.

Can Inhaled Anesthetic Agents Be Given Safely to Patients in the ICU?

The use of inhaled anesthetic agents for sedation in the ICU is currently not routine and may give rise to some concerns. The delivery of inhaled anesthetic agents *via* modern ICU ventilators is not straightforward, and other concerns include ambient pollution in the ICU setting and the different traditions of anesthesia-trained *versus* nonanesthesia-trained ICU physicians.[32,33] Use of inhaled agents requires that practitioners be familiar with the physiologic effects and pharmacologic properties of these agents.

Delivery of Inhaled Anesthetic Agents via *Modern ICU Ventilators*

Historically, delivery of inhaled anesthetic agents in the ICU has been possible using, among others, the Siemens 900C ventilator (Siemens-Elema; Maquet AB, Solna, Sweden) with a compatible vaporizer. However, modern, commercially available ICU ventilators do not have vaporizers, making delivery cumbersome with different adaptations that have been described.[34] In our case, a miniature vaporizer, the AnaConDa®, was used (fig. 1).[13] The device enables delivery of inhaled anesthetics in the ICU and with any ventilator. It is a modified heat-moisture exchanger with a vaporizer rod and an adsorbing active carbon filter. The device is placed between the Y-piece of the respiratory circuit and the endotracheal tube and has an outlet for gas sampling (fig. 1). Anesthetic liquid is infused from a syringe pump and vaporized passively in the device during inspiration. Approximately 90% of the exhaled anesthetic agent is adsorbed by the active carbon filter and recycled to the patient with the next breath. The remaining anesthetic agent passes the filter and leaves the expiratory outlet of the ventilator where it can be scavenged. The desired inspiratory and end-tidal concentrations are acquired by adjustment of the infusion rate of isoflurane/sevoflurane to the AnaConDa®. The AnaConDa® has a total volume of 100 ml, exceeding that of most standard heat-moisture exchangers, and in our experience, the increased dead space precludes its use as designed in small patients, typically less than 30 kg. In small adults and children, an alternate placement at the inspiratory limb with no rebreathing has been described.[35] The AnaConDa® is only commercially available in the European Union. Desflurane cannot be administered *via* the AnaConDa® because of its low boiling point. Anesthesia machines are becoming increasingly refined, and a future development may be adult and pediatric ICU ventilators with the possibility of delivering and scavenging anesthetic agents.

Environmental Aspects of Inhaled Anesthetic Agents in the ICU Setting

During inhaled sedation, scavenging of waste gas can be performed actively or passively. Gas from the ventilator and the gas analyzer can be led to a central evacuation system or to a specially designed, commercially available, active carbon canister. Studies of ambient anesthetic gas concentrations during inhaled isoflurane and sevoflurane sedation have demonstrated concentrations lower than the recommended exposure limits.[20,36] Recommended exposure limits vary between countries but are typically between 2 and 50 ppm for long-term exposure, and concentrations less than these thresholds have not been associated with risks of staff toxicity. Animal toxicity has been demonstrated at no less than 6,000 ppm (0.6%) with congenital malformations in mice exposed to these concentrations of isoflurane daily during the early phases of pregnancy.[37]

Anesthesia Training and Inhaled Anesthetic Agent Delivery in the ICU Setting

The vast majority of Swedish ICU physicians are anesthesia-trained, making them familiar with inhaled anesthetic agents, gas concentration monitoring, and the minimum alveolar concentration concept. In other settings, nonanesthesia-trained ICU physicians may be reluctant or possibly not even permitted to use this therapeutic option for sedation of ICU patients. Although propofol has been readily adopted from the anesthesia setting into the ICU, inhaled anesthetics may be more strongly linked to anesthesiology as a medical discipline.[32,33] However, general anesthesia can be achieved with an intravenous anesthetic drug, such as propofol, and sedation can be achieved with an inhaled anesthetic agent. Delivery and elimination routes are probably more notable differences between intravenous and inhaled anesthetics than the pharmacodynamic profiles. Another difference of note is the ability to

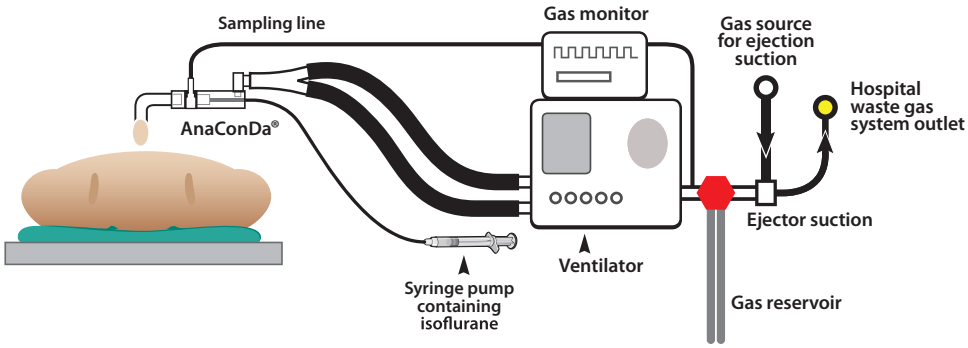

Fig. 1. Schematic representation of the adapted respiratory circuit, including the AnaConDa®, between to endotracheal tube and the Y-connector to administer the inhaled anesthetics isoflurane or sevoflurane. The system includes aspects not generally found in the intensive care unit setting: (1) gas sampling and monitoring to easily adjust administered concentration/dose to achieve desired end-tidal concentration and (2) a scavenging system for elimination of anesthetic agent leaving the circuit (AnaConDa®; Sedana Medical AB, Stockholm, Sweden). Modified, with permission, from Sackey PV, Martling CR, Granath F, Radell PJ: Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Criti Care Med 2004; 32:2241–6.[13]

monitor inhaled anesthetic agent concentrations online. With repeated in-house training of all staff, the 6-yr experience of inhaled isoflurane sedation for selected patients in our general ICU has been uneventful, with titration and monitoring performed mostly by nonanesthesia-trained nursing staff. In countries with more diverse background training, there may be need for a close working relationship between nonanesthesia-trained intensivists and anesthesiologists for inhaled anesthetic agent sedation to be considered a therapeutic option for ICU patients.

"One Size Fits All" or Tailored Sedation: A Role for the Anesthesiologist?

Although patient comfort and safety may be the main goals of sedation, the axiom *primum non nocere* needs also to be borne in mind at all times. The choice of sedative treatment and monitoring is being acknowledged as a decision with great implications for the outcome of critically ill patients.[38] High doses of midazolam may be necessary to sedate a child but may lead to several days of prolonged ventilator treatment in an elderly patient or a patient with renal and liver dysfunction. Specific electrocardiogram changes may contraindicate the use of haloperidol or α_2-agonists. Young age and sepsis may make the use of high doses of propofol unsuitable. To avoid iatrogenic adverse/prolonged effects of sedative agents and analgesics, awareness of how critical illness and multiple organ failure affect the pharmacodynamics and pharmacokinetics of the drug is central (see table 1). For example, vasodilating effects of inhaled agents may have both positive and negative effects in various critical care settings and must be considered in the individual clinical context. Our experience, however, has been that the hemodynamic effects of isoflurane at sedation doses are generally mild and rarely preclude their use. Consideration of pharmacokinetic and pharmacodynamic aspects in the individual case is a critical part of daily anesthesiology practice.

Different drug management strategies have been proven to reduce iatrogenic oversedation, with documented clinical outcome benefits. These strategies include drug rotation,[12] goal-directed frequent drug dose titration,[39] daily sedative and analgesic interruption,[40] combined sedative interruption and spontaneous breathing tests,[41] and pain monitoring.[42] Thus, physicians are not only challenged in what drugs to use but also on how administration and discontinuation are managed. As the patient's status changes during the ICU stay, vigilance is necessary to adapt treatment promptly to best provide comfort and safety without harming the patient. In a Canadian survey of ICU sedation routines, patients were more likely to be treated with a protocol and sedation scale if the ICU physician had anesthesia training compared with a nonanesthesia-trained ICU physician.[4]

A broad arsenal of therapeutic options—including intravenous and inhaled anesthetic agents—combined with active decisions, based on patient needs and ongoing treatments, is likely to improve sedation-related outcomes for ICU patients. A future scenario should possibly be to create a tailored sedation and analgesia plan (fig. 2) for each patient at the outset of sedative use, revisited during the course of the treatment. In some countries with division of anesthesia and

Table 1. Main Advantages and Disadvantages of Various Agents Used for ICU Sedation

Drug or Drug Class	Main Advantages	Main Side Effects/Risks
Benzodiazepines (midazolam/lorazepam)	Relative hemodynamic stability Amnesia Anticonvulsant Long experience and safety profile	Prolonged/unpredictable duration due to drug accumulation/organ failure Delirium/postsedation agitation Tolerance and withdrawal with prolonged use
Propofol	Relatively short-acting No marked change of elimination in hepatic or renal failure Reliable dose-effect relation	Hemodynamic effects Hyperlipidemia Propofol infusion syndrome
Inhaled anesthetic agents (isoflurane, sevoflurane, desflurane)	Short-acting Elimination independent of hepatic or renal function Monitored drug concentration	Hemodynamic effects Malignant hyperthermia Unclear effects with prolonged use
α_2-Agonists	Reduced autonomic stress response Minimal respiratory depression Rousability	Insufficient for deep sedation Bradycardia/hypotension
Haloperidol	Reduced motor agitation	Extrapyramidal side effects Long-QT-syndrome/arrythmias
Opiates	Pain relief Mild sedation	Respiratory depression Gut immobility Tolerance and withdrawal with prolonged use

ICU = intensive care unit.

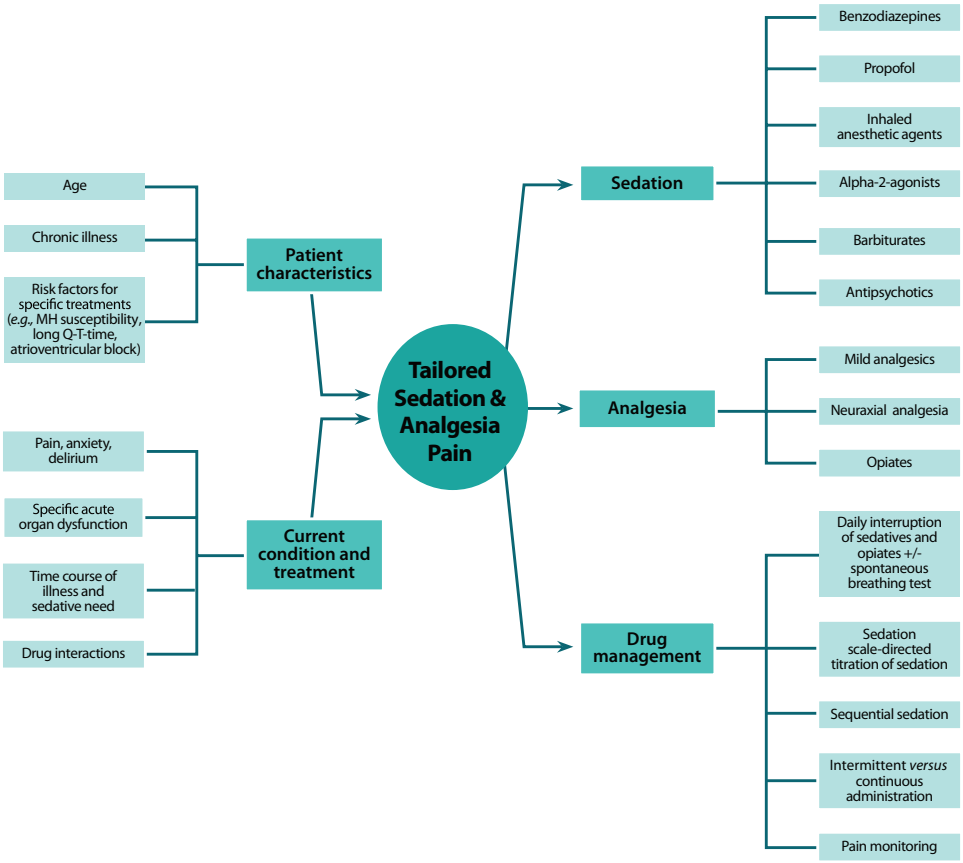

Fig. 2. A suggested approach for tailoring sedation and analgesia in intensive care unit patients. This approach includes consideration of the patient's unique characteristics as well as the special requirements of different critical care illnesses in determining and executing a plan for sedation, including the various available drug classes and sedation techniques. MH = malignant hyperthermia.

critical care, it may be that these two worlds need to converge to reach this goal of tailored sedation for the critically ill patient.

Knowledge Gap and Future Research

Although long-tem inhaled sedation in adult ICU patients is promising so far, potential toxicity of long-term (days-weeks) exposure to inhaled anesthetic agents has not been studied systematically, and currently, relatively few patients have been exposed to such long-term treatment. Currently, the use of inhaled sedation for ICU patients is off-label. Further research is needed to investigate potential long-term toxicity, as well as cost-benefit aspects, before inhaled anesthetic agents can be more widely used. In children, some data indicate that there are reversible neurologic symptoms after isoflurane sedation.[35,43] The youngest children appear to be at greatest risk of ataxia, tremor, and clonus, symptoms that subside within days.[43] The clinical significance of these transient motor symptoms is currently unclear and needs to be studied, as well as the possible occurrence with other anesthetics and sedatives.

Furthermore, safety issues regarding different anesthetic agent delivery methods (for example, the AnaConDa® *vs.* conventional vaporizer technique) in adults and children need further study.

Although future studies comparing the efficacy and safety profiles of new sedative agents are needed, different drug management strategies with similar benefit also need comparison. For example, there is no study comparing regular titration of sedation[39] and daily interruption of sedatives.[40]

Long-term outcome after sedation has recently come into focus.[23,44,45] Besides immediate efficacy and side effects, long-term patient-reported outcomes—including aspects such as recovery of cognitive functions, ICU memory panorama, and psychologic morbidity after different sedative drugs or regimens—should be an integral part of future ICU sedation trials.

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ANESTHESIOLOGY REFLECTIONS

A Taste of Sim's *Heritage of Anesthesia*

From the very beginning of his library career back in 1971, Patrick Pui-Kam Sim, M.L.S. (1939–2010), was enchanted by antiquarian books housed at the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. Photographed on the left (in 1991) and on the right (in 2004) by the curator, "Pat" Sim relished his every moment in the K. Garth Huston, Sr. Rare Book Room. Leafing through the old tomes, Pat resolved that, one day, he would annotate a bibliography with essential information gleaned from each revered volume. Before terminal illness claimed the life of the Paul M. Wood Distinguished Librarian Emeritus, Patrick Sim would taste a cake decorated by the curator's wife with the title Pat had planned for his masterwork, *Heritage of Anesthesia*, a publication that he would never live to see. . .. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.