

## Sedation and Analgesia in the Intensive Care Unit

John P. Kress, Anne S. Pohlman, and Jesse B. Hall

Department of Medicine, University of Chicago, Chicago, Illinois

Critically ill patients requiring mechanical ventilation are frequently treated with sedatives and analgesics. Much of what is known about these medications is derived from investigations in the operating room, an environment often very different from the intensive care unit (ICU). Recently, important complications related to sedation practices in the ICU have been recognized and efforts to modify sedation practices in the ICU have begun. Sedation practices vary widely between institutions, partly because of institutional bias and partly because requirements for sedation vary greatly from patient to patient. This commentary discusses principles and goals of sedation in the ICU based on data from publications on this topic. Certainly, some patients in the ICU require little or no sedation. Nonpharmacological means (e.g., patient reassurance, positioning comfortably in bed) should be attempted initially in all patients; however, this commentary focuses on patients who require mechanical ventilation and pharmacological means of sedation. This commentary does not review individual medications for sedation and analgesia; the reader is referred to guidelines by Jacobi and coworkers (1) for a review of this topic.

### INDICATIONS FOR SEDATION

Pain is a common experience for most ICU patients (2–4). Failure to recognize that pain frequently leads to agitation may result in excessive administration of sedatives. Accordingly, an aggressive approach to managing pain has been strongly recommended by published consensus opinions regarding sedation in the ICU (1, 5). This can be challenging because many clinical parameters such as changes in vital signs may be unreliable indicators of the presence of pain. Surgical incisions, indwelling vascular catheters, endotracheal suctioning, and mechanical ventilation are all potential sources of pain for patients. Pain may result in many adverse events including increased endogenous catecholamine activity, myocardial ischemia, hypermetabolic states, and anxiety. A compelling study of mechanically ventilated preterm neonates reported a decrease in morbidity and mortality in those receiving morphine rather than midazolam or placebo, underlining the importance of pain control in critical illness (6). Previous studies have shown that benzodiazepines may enhance the analgesic effects of opiates (7, 8), a phenomenon not seen with propofol. Indeed, we have previously noted that opiate requirements are decreased in patients sedated with benzodiazepines rather than propofol (9). Nevertheless, seda-

tives should never be given as a substitute for adequate analgesia. A strategy that strives to focus initially on assuring adequate analgesia will often reduce the need for other sedatives in many critically ill patients. Accordingly, patients should be frequently reassessed to assure that pain is being adequately addressed.

Although pain is certainly a cause for anxiety in most ICU patients, many patients suffer from anxiety even after analgesia is addressed. It is self-evident that being critically ill and dependent on others for care can invoke anxiety. Accordingly, sedation strategies must recognize and respond to this problem.

Dyspnea is common in ICU patients and may be a source of distress. Coughing is common in intubated patients, particularly during suctioning. Excessive coughing may contribute to patient-ventilator dyssynchrony. Opiates may alleviate coughing in intubated patients.

Excessive oxygen consumption ( $\dot{V}O_2$ ) may be detrimental in patients with respiratory failure or shock. A shift of the delicate balance of oxygen delivery and consumption can be an important component of the management of these patients. Previous work has shown that oxygen consumption can be reduced from baseline by an average of 15% after administration of sedatives and opiates (9). For some patients, such as those with shock or severe hypoxemic respiratory failure, this reduction in oxygen consumption may be important for cardiopulmonary stability.

Although it may seem intuitive that amnesia for the period of critical illness is desirable, data supporting this notion are lacking. On the contrary, it has been our experience that the absence of memory of a period in a person's life may be unsettling for some, even if that period is the experience of critical illness. The notion that complete amnesia may be detrimental has been supported by some studies (10–12). Accordingly, we believe the only circumstance in which complete amnesia is mandatory is during the administration of neuromuscular blocking agents. Certainly, more data are needed to improve our understanding of the impact of sedation and amnesia on long-term psychological outcomes in critically ill patients.

Some patients may demonstrate periods of disorientation during which psychotic behavior occurs. At times an aggressive type of behavior may ensue. Reasons for such behavior include medications, sepsis, fevers, encephalopathy (hepatic or renal), paranoia, or withdrawal syndromes (alcohol, tobacco, or other illicit drugs).

Work by Ely and colleagues reported an 83% incidence of delirium in a cohort of ICU patients. Delirium is characterized by an acutely changing or fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation (13). Treatment of such agitated behavior is another indication for sedation in the ICU. Such behavior often responds well to neuroleptic medications such as haloperidol (1).

### ASSESSING ADEQUACY OF SEDATION

Assessing adequacy of sedation can be difficult because of its subjective nature. Several objective sedation scales such as the

(Received in original form April 1, 2002; accepted in final form July 16, 2002)

Correspondence and requests for reprints should be addressed to John P. Kress, M.D., Section of Pulmonary and Critical Care Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 6026, Chicago, IL 60637. E-mail: jkress@medicine.bsd.uchicago.edu

Am J Respir Crit Care Med Vol 166. pp 1024–1028, 2002

DOI: 10.1164/rccm.200204-270CC

Internet address: www.atsjournals.org

Ramsay Sedation Scale (14) and the Sedation-Agitation Scale (15) have been developed. The Ramsay scoring system is one of the most commonly used scales. Although it has the benefit of simplicity, it does not effectively measure quality or degree of sedation with regard to the goals outlined above (16) and has never been objectively validated (17). Newer sedation scales are reported to show improvements in validity and reliability (15, 18).

The evaluation of sedation adequacy is a bedside maneuver. The nurse's input is critical, because he or she will often notice changes from an optimal level of sedation. Ideally, one would prefer a patient with all of the indications for sedation outlined above met, yet fully communicative with bedside caregivers. Such a state of sedation correlates with a Ramsay score of 2 or 3 or a Sedation-Agitation Scale score of 3 or 4 (14, 15). This state of being awake and communicative while sedatives are still infusing is achievable in some patients. We previously demonstrated that with sedation based on midazolam and morphine infusions, about 60% of our patients were able to follow commands with the sedatives infusing (awake at "time zero"). Likewise, about 30% of patients sedated with propofol and morphine infusions were able to follow commands while the sedatives were infusing (9). Others, however, must be sedated to such a point that constant communication is not possible. For such patients, we have previously reported a set of end points for assessing recovery from sedation when the drugs are stopped. Asking the patient to (1) open eyes to verbal command, (2) follow the bedside observer with eyes, (3) hand grasp on command, and (4) stick out tongue on command was found to be simple, quick, objective, and reproducible between blinded and unblinded observers (9).

The Bispectral Index monitor, a device that processes the raw electroencephalogram signal into a discrete scaled number, has been evaluated as a tool to monitor sedation in the ICU setting. Some have found this device to reliably detect a patient's level of consciousness under general anesthesia (19), although others have questioned the overall utility of this device for preventing awareness (20). Although preliminary data in the ICU setting suggest a good correlation between the Bispectral Index and the Sedation-Agitation Scale (21), this device has undergone limited evaluation in the ICU and awaits more extensive validation before its role in the ICU setting is established (1).

## STRATEGIES FOR ADMINISTERING SEDATIVES IN THE ICU

Because no single drug can achieve all the indications for sedation and analgesia in the ICU, a combination of drugs, each titrated to specific end points, is typically a more effective strategy. A combination strategy may allow lower doses of individual drugs and reduce problems of drug accumulation. Sedatives and analgesics can be administered either by intermittent bolus dosing or by continuous infusion. The former may result in periods of both oversedation and undersedation and increased demands on nursing time. Indeed, for many critically ill patients requiring aggressive levels of sedation, this approach may be extremely taxing on the bedside nurse and potentially distract nursing attention away from other patient care issues. However, a study by Kollef and colleagues reported that continuous intravenous sedation was associated with prolongation of mechanical ventilation, ICU and hospital length of stay, organ system failure, and reintubation rates when compared with intermittent sedation strategies or no sedation (22). An important limitation of this study was the lack of randomization of patients. Indeed, no prospective, randomized trial of continuous sedative infusions versus intermittent bolus infusions has been done. Nevertheless, this study alerted clinicians to the important and perhaps under-

recognized complications accompanying continuous sedative infusions in the ICU. Purported benefits of continuous sedative infusions include a more consistent level of sedation with greater levels of patient comfort. The perceived convenience this strategy provides to both patients and caregivers is likely the greatest reason for its popularity.

Ideally, sedation of critically ill patients would be optimized if strategies that attended to pharmacokinetic and pharmacodynamic profiles commonly observed in such patients were well understood and described, and in turn provided specific guidance for drug administration. Unfortunately, critically ill patients frequently exhibit unpredictable alterations in these profiles (23). Early work reporting short half-lives of benzodiazepines such as midazolam and lorazepam was derived from brief administration (24). In this setting, rapid recovery of consciousness was the norm (25). It was on the basis of these experiences that the use of these drugs was extrapolated to the ICU. Clinical experience with critically ill patients has, however, revealed a much different pattern than that reported in the operating room or procedure suite (26–28), and accumulation of sedatives in the ICU remains a major problem (22). Critically ill patients may have altered hepatic and/or renal function that impairs drug clearance (29). Drug–drug interactions, altered protein binding, and circulatory instability are common. In the ICU, sedatives typically exhibit multicompartmental pharmacokinetics with a tendency for accumulation in the peripheral compartment and resulting prolongation of clinical effect. Titration of drugs against clinical end points can be extremely imprecise. This is particularly so, given that the two extremes of sedation (extreme agitation versus drug-induced coma) are so dramatically different. For busy clinicians, a state of drug-induced coma may be more acutely desirable than unmanageable agitation and it is often natural to "overshoot" when sedating agitated patients. Few would dispute that the impetus for aggressive sedation of agitated patients early in the course of critical illness (e.g., stabilization initially on the ventilator) is rational and appropriate.

A quandary that faces clinicians daily is the conflict between providing the deep level of sedation often needed to meet the goals outlined above while preventing the seemingly inevitable drug accumulation that accompanies such a level of sedation. Despite efforts to minimize the amount of sedative administered, many patients with respiratory failure require doses of sedatives that are much greater than quoted in the literature and recommended by drug manufacturers (30). On occasion, these patients may even require pharmacological paralysis (31).

There is much excitement among practitioners as new, innovative strategies have been reported to result in improved outcomes for many patients, including common conditions such as sepsis (32, 33), acute renal failure (34), acute respiratory distress syndrome (35), status asthmaticus (36), and cancer (37). To accomplish these improved outcomes, unconventional strategies and procedures are often required. Such "unconventional" management includes ventilator strategies employing permissive hypercapnia, low tidal volumes, prone positioning, and pressure-controlled ventilation. These strategies may be inherently distressing to many patients. As the level of illness acuity increases, it may become difficult to reconcile the goals of assuring patient tranquility while preventing accumulation of sedatives. Indeed, attempts to minimize the amount of sedative *initially* administered may result in severe levels of anxiety and agitation with accompanying cardiopulmonary instability. Such instability may manifest itself as extreme hypertension, tachycardia, tachypnea, ventilator dyssynchrony, hypoxemia, and unplanned extubations (38). For these patients, it becomes apparent that early deep sedation is the only practical solution.

The inability to follow a patient's mental status through the

course of critical illness is an important drawback of deep sedation. Acute organ failure is a common complication of critical illness. Ideally, a head-to-toe daily assessment for the presence of organ failures should be routine for every critically ill patient. This is particularly so during resuscitative phases of ICU care, when assessing the adequacy of end organ perfusion and function is of paramount importance. Because of the potential long-term consequences of brain injury, acute cerebral dysfunction is particularly disconcerting to all clinicians caring for critically ill patients. Nevertheless, many patients kept under the veil of sedation may be unable to be assessed neurologically. A noncommunicative, critically ill patient may develop unrecognized intracranial, intrathoracic, or intra-abdominal catastrophes. Communication and thorough physical examination may detect such problems early on and obviate urgent diagnostic studies and therapeutic interventions after a problem has advanced.

A protocol-driven approach to sedation may help navigate these dilemmas. Brook and colleagues noted a significant reduction in the duration of mechanical ventilation, ICU and hospital length of stay, and the need for tracheostomy among ICU patients with acute respiratory failure when sedatives were administered by nurses according to a written protocol (39). The protocol required an initial assessment of analgesic needs. A Ramsay Sedation Scale score of 3 was targeted (patient awake, responds to commands only [14]). If frequent (more than every 2 hours) rebolus administration of opiates (fentanyl) or benzodiazepines (lorazepam) was required, continuous infusions of these drugs were started. Reassessment every 4 hours and downward titration of infusion rates were targeted until the infusion(s) was (were) stopped.

We have described how daily interruption of sedative infusions can reduce many of the complications of sedation in the ICU setting (40). We evaluated patients who received either midazolam and morphine or propofol and morphine by continuous infusion. Patients were randomized to a daily scheduled interruption of the sedative and opiate infusions versus infusions managed by the primary ICU team without a mandatory daily interruption. In the interruption group, the duration of mechanical ventilation was reduced by 2.5 days and ICU length of stay was reduced by 3.5 days. Furthermore, we noted a significant reduction in diagnostic studies to investigate unexplained alterations in mental status. In the control group, 27% of patients underwent brain computed tomography, brain magnetic resonance imaging, or lumbar puncture to investigate causes of mental status changes. In contrast, the sedative interruption group had only 9% of patients undergo such studies. In addition, only 25% of the patients in the control group had a test result that explained their mental status changes, as opposed to half of the patients in the sedative interruption group. The patients in the sedative interruption group spent the vast majority of their ICU days awake and able to follow commands (average of 86% of ICU days) compared with the control group patients, who averaged only 9% of their ICU days awake and able to follow commands. The amount of midazolam and morphine administered was also significantly reduced in the group of patients who underwent daily sedative interruption.

The strategy of daily sedative interruption allowed a focused downward titration of sedative infusion rates over time, streamlining administration of these drugs and minimizing the tendency for accumulation. On the basis of this study, we believe that one approach to optimizing patient outcome is a daily interruption of sedative infusions to permit physician and patient communication to take place and to facilitate the physical examination.

Exceptions to this recommendation include patients requiring muscle paralysis, who should never be awakened from sedation until the paralytic agent has worn off. In this group, daily or

even twice daily interruption of neuromuscular blockade is advisable to assess the adequacy of sedation and analgesia and the ongoing need for neuromuscular blockade. In addition to this, patients at high risk for myocardial ischemia could conceivably have ischemia precipitated by sedative interruption. More data are needed to improve our understanding of the risks of routine sedative interruption in such patients. Patients in surgical ICUs were not included in our study, and therefore the risks and benefits of daily sedative interruption in this population are not known.

The “wake-up” period is a time when the depth of sedation can be evaluated and adjusted to individual patient needs. The protocol-driven approach to sedation advocated by Brook and colleagues likewise allows optimization of sedative administration to meet patient needs (39). Often, after an assessment of patient sedation needs, it becomes apparent that depth of sedation can be decreased without compromising the stated goals of sedation. Indeed, we believe this strategy allows clinicians to minimize the problem of sedative accumulation and, rather, to use this accumulation of sedatives to their advantage. Even when sedative infusions are stopped every day, there is some drug accumulation in adipose tissue. Initially, the thought of decreasing or discontinuing the sedative infusion in a critically ill patient for whom it has been difficult to achieve a state of tranquility may be unsettling. We have noted a tendency for clinicians to aggressively sedate patients early in their ICU course and to keep the same level of deep sedation continuing indefinitely. A daily holiday from sedatives allows for clinician evaluation of neurological function as well as an opportunity for testing the sedative needs for each patient on a daily basis. It eliminates the tendency to “lock in” to a high sedative infusion rate, which—while appropriate on the first ICU day—may no longer be needed on subsequent days. Because sedatives do accumulate even when the infusions are stopped each day, we take advantage of this pharmacological property. By turning sedative infusions down or off, tissue stores can redistribute drug back into the circulation. This leads to a common scenario in which patients experience delays in recovery of mental status in spite of the sedatives being decreased or discontinued. Certainly, there are times when the interruption of sedative infusions leads to abrupt awakening and agitation. This potential situation must be anticipated by the ICU team to avoid complications such as patient self-extubation. Therefore, communication between nurses and physicians is essential. The timing of sedative discontinuation must be initiated by the nurse as a part of his or her daily patient assessment routine. Sedative interruption does not always result in a successfully awakened and communicative patient. Indeed, excessive agitation (more commonly seen early in the course of severe critical illness) should lead to cessation of the wake-up attempt. Although the attempt at waking and communicating with the patient may be declared a failure on a given day, this does not portend inevitable failure on all subsequent days. Accordingly, such a strategy may be repeated each day and the rate of sedative infusions decreased as tolerated. When awakening patients, initially we seek only to bring patients to the brink of consciousness—able to follow simple commands (open eyes, squeeze hand, track with eyes, open mouth/stick out tongue—equivalent to the Ramsay Sedation Scale score of 3 targeted by Brook and colleagues) without precipitating excessive agitation. Once objective signs of consciousness are demonstrated, restarting sedatives as needed is recommended. If after discontinuing the sedative infusion, the patient requires re sedation, we recommend restarting the infusion at 50% of the previous dose. Adjustments from this starting point can then be made as required. In reviewing data from our sedative interruption study, only 32% of our patients required re sedation because of agitation that

occurred without successful awakening. Within this subgroup, an average of 34% of the attempted wake-ups per patient were unsuccessful. It is worth noting that the use of the term “awakening” is probably inaccurate, because most critically ill patients do not exhibit normal sleep patterns (41). We use this term to indicate an emergence to consciousness from a state of drug-induced acute mental status changes.

While it is clear that protocol-driven sedation can improve patient outcomes, it is important to recognize that a treatment protocol is a guide to therapy and cannot address every clinical situation (42). Limitations of protocol-directed studies include potential lack of generalizability (e.g., single center with house staff setting may be different than a community setting), lack of blinding, lack of reporting of “other” outcomes such as long-term follow-up, and uncertainty about level of compliance needed to assure desired outcomes (43). Clearly, a multidisciplinary, cooperative approach is necessary to assure compliance and successful implementation of protocols.

Previous studies have noted that propofol may be associated with a more rapid wake-up than benzodiazepines. The rapid recovery from propofol may be attenuated by concomitant administration of opiates for analgesia, however. Indeed, patients receiving prolonged administration of sedatives may develop tolerance and require escalating doses over time (44, 45). Withdrawal symptoms may be seen in patients receiving prolonged infusions of sedatives. Katz’s group noted a high incidence of withdrawal in infants receiving fentanyl in either high doses or for prolonged time periods (46). Cammarano and colleagues noted a 32% incidence of withdrawal in adults receiving opiate, benzodiazepine, and propofol infusions. This tended to be associated with higher doses of these sedatives, with a trend toward occurrence with more rapid weaning of drugs (47). The diagnosis of sedative or opiate withdrawal in critically ill ICU patients can be challenging. Many of the established signs of withdrawal (tachycardia, hypertension, fever, tachypnea, pupillary dilation, agitation, delirium, seizures) are nonspecific, commonly observed phenomena in critically ill patients. Likewise, many established symptoms are either nonspecific (restlessness, irritability, increased sensitivity to pain, nausea, dysphoria, insomnia, and anxiety) or difficult to elicit from mechanically ventilated patients (opioid craving, cramps, muscle aches, increased sensitivity to light and sound, paresthesia, strange sensations). We often convert patients who receive opiates for more than 1 week to methadone in anticipation of potential withdrawal. Likewise, patients receiving benzodiazepine infusions sometimes require gradual tapering of these drugs. It is interesting to note that patients in studies reporting withdrawal signs and symptoms did not undergo daily interruption of sedative infusions. Anecdotally, we have not noted withdrawal syndromes to be a common problem in patients subjected to daily sedative interruption. However, we did not formally assess patients for this complication in our previous study (40). Certainly, this anecdotal observation should be more formally evaluated before daily interruption of sedative infusions is alleged as a means of minimizing drug withdrawal complications.

It is clear that sedatives may impact the duration of mechanical ventilation (39, 40). The reduction in duration of mechanical ventilation that Brook and coworkers and we observed was likely related to earlier recognition of patient readiness to undergo a spontaneous breathing trial. Others have reported previously an important link between a successful spontaneous breathing trial and subsequent liberation from mechanical ventilation (48, 49). Accordingly, we believe the use of a spontaneous waking trial, followed when possible by a spontaneous breathing trial, should be implemented widely in the care of critically ill patients requiring mechanical ventilation.

## FUTURE DEVELOPMENTS

It is clear that much remains to be learned about optimizing sedation and analgesia in critically ill patients. Better methods for assessing patients for adequacy of sedation and analgesia are needed. Objective monitors such as the Bispectral Index may prove to be useful, although more data are needed before widespread use of devices such as these can be recommended. Newer drugs with lesser tendencies toward accumulation (e.g., remifentanyl, dexmedetomidine) may also find a place if evidence of improvements in patient outcomes is demonstrated. Perhaps more importantly, however, improvements in strategies for administering sedatives and analgesics must be investigated. Sedation protocols such as nursing-directed protocols or daily sedative interruption must be further studied so that improvements of such existing protocols, as well as development of new sedation strategies, can take place.

## Conclusion

Sedation is an important component of the treatment of mechanically ventilated, critically ill patients. There are currently a wide variety of pharmacological agents available for the diverse needs of this heterogeneous group of patients. Directing treatment to specific and individualized goals will assure that patient needs are met. All currently available sedatives for use in the ICU have limitations. We reported no important differences in any important patient outcomes when comparing different classes of drugs as long as a strategy directed at limiting complications of drug accumulation was adhered to (50). Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be utilized.

## References

- Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002;30:119–141.
- Novaes MA, Knobel E, Bork AM, Pavao OF, Nogueira-Martins LA, Ferraz MB. Stressors in the ICU: perception of the patient, relatives and healthcare team. *Intensive Care Med* 1999;25:1421–1426.
- Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung* 1990;19:526–533.
- Turner JS, Briggs SJ, Springhorn HE, Potgieter PD. Patients’ recollection of intensive care unit experience. *Crit Care Med* 1990;18:966–968.
- Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, Schein RM, Spevetz A, Stone JR. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med* 1995;23:1596–1600.
- Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med* 1999;153:331–338.
- Bianchi M, Mantegazza P, Tammiso R, Zonta N, Zambotti F. Peripherally administered benzodiazepines increase morphine-induced analgesia in the rat: effect of RO 15-3505 and FG 7142. *Arch Int Pharmacodyn Ther* 1993;322:5–13.
- Sivam SP, Ho IK. GABA in morphine analgesia and tolerance. *Life Sci* 1985;37:199–208.
- Kress JP, O’Connor MF, Pohlman AS, Olson D, Lavoie A, Toledano A, Hall JB. Sedation of critically ill patients during mechanical ventilation: a comparison of propofol and midazolam. *Am J Respir Crit Care Med* 1996;153:1012–1018.
- Jones C, Griffiths RD. Disturbed memory and amnesia related to intensive care. *Memory* 2000;8:79–94.
- Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit Care Med* 2001;29:573–580.
- Kress JP, Lacy M, Pliskin N, Pohlman A, Hall JB. The long term psycho-

- logical effects of daily sedative interruption in critically ill patients. *Am J Respir Crit Care Med* 2001;163:A954.
13. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–2710.
  14. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974;3:656–659.
  15. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med* 1999;27:1325–1329.
  16. Crippen DW. Neurologic monitoring in the intensive care unit. *New Horiz* 1994;2:107–120.
  17. Hansen-Flaschen J, Cowen J, Polomano RC. Beyond the Ramsay Scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Crit Care Med* 1994;22:732–733.
  18. Sessler CN, Gosnell M, Grap MJ, Brophy GT, O'Neal PV, Tesoro E, Elswick RK. A new Agitation-Sedation Scale for critically ill patients: development and testing of validity and inter-rater reliability. *Am J Respir Crit Care Med* 2000;161:A506.
  19. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997;86:836–847.
  20. O'Connor MF, Daves SM, Tung A, Cook RI, Thisted R, Apfelbaum J. BIS monitoring to prevent awareness during general anesthesia. *Anesthesiology* 2001;94:520–522.
  21. Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. *Crit Care Med* 1999;27:1499–1504.
  22. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest* 1998;114:541–548.
  23. Bodenham A, Shelly MP, Park GR. The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. *Clin Pharmacokinet* 1988;14:347–373.
  24. Wagner BKJ, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet* 1997;33:426–453.
  25. Dundee JW, Samuel IO, Toner W, Howard PJ. Midazolam, a water soluble benzodiazepine: studies in volunteers. *Anaesthesia* 1980;35:454–458.
  26. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolize midazolam. *Anaesthesia* 1987;42:619–626.
  27. Byatt CM, Lewis LD, Dawling S, Cochrane GM. Accumulation of midazolam after repeated dosage in patients receiving mechanical ventilation in an intensive care unit. *BMJ* 1984;289:799–800.
  28. Malacrida R, Fritz ME, Suter PM, Crevoisier C. Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. *Crit Care Med* 1992;20:1123–1126.
  29. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet* 1997;32:210–258.
  30. Oldenhof H, de Jong M, Steenhoek A, Janknegt R. Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? *Clin Pharmacol Ther* 1988;43:263–269.
  31. Gottlieb JE, Park P, Girod A, Ancukiewicz M, Schoenfeld DA. Comparison of neuromuscular blocker and sedative use among patients with ARDS treated with low versus high tidal volume. *Am J Respir Crit Care Med* 2000;161:A506.
  32. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, *et al*. Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
  33. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.
  34. Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002;346:305–310.
  35. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
  36. Tuxen DV, Williams T, Scheinkestel C. Limiting dynamic hyperinflation in mechanically ventilated patients with severe asthma reduces complications. *Anaesth Intensive Care* 1993;21:718.
  37. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med* 1996;125:625–633.
  38. Boulain T. Association des Reanimateurs du Centre-Quest: unplanned extubations in the adult intensive care unit. *Am J Respir Crit Care Med* 1998;157:1131–1137.
  39. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999;27:2609–2615.
  40. Kress JP, Pohlman A, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342:1471–1477.
  41. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000;117:809–818.
  42. Park G, Coursin D, Ely EW, England M, Fraser GL, Mantz J, McKinley S, Ramsay M, Scholz J, Singer M, *et al*. Commentary: balancing sedation and analgesia in the critically ill. *Crit Care Clin* 2001;17:1015–1027.
  43. Ibrahim EH, Kollef MH. Using protocols to improve the outcomes of mechanically ventilated patients: focus on weaning and sedation. *Crit Care Clin* 2001;17:989–1001.
  44. Shafer A, White P, Schuttler J, Rosenthal MH. Use of fentanyl infusion in the intensive care unit: tolerance to its anesthetic effects? *Anesthesiology* 1983;59:245–248.
  45. Busto U, Sellers E. Pharmacologic aspects of benzodiazepine tolerance and dependence. *J Subst Abuse Treat* 1991;8:29–33.
  46. Katz R, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med* 1994;22:763–767.
  47. Cammarano WB, Pittet JF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* 1998;26:676–684.
  48. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335:1864–1869.
  49. Kollef MH, Shapiro SD, Silver P, St. John RE, Prentice D, Sauer S, Ahrens TS, Shannon W, Baker-Clinkscale D. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997;25:567–574.
  50. Kress JP, Pohlman AS, Hall JB. Effects of sedative interruption in critically ill, mechanically ventilated patients receiving midazolam or propofol. *J Clin Outcomes Manage* 2001;8:33–39.