Sedation, analgesia, and neuromuscular blockade for high-frequency oscillatory ventilation

Curtis N. Sessler, MD, FCCM, FCCP

Objective: To provide a comprehensive review of the issue related to the administration of sedative, analgesic, and neuromuscular blocking agents (NMBA) to patients who are receiving ventilatory support for acute respiratory distress syndrome (ARDS) with high-frequency oscillatory ventilation.

Results: Sedative, analgesic, and NMBA are used with great frequency in patients with severe ARDS who are undergoing high-frequency oscillatory ventilation. In particular, the use of NMBA has been higher than for other ARDS populations. Important considerations for effective treatment include careful patient evaluation, patient-based medication selection, identification of treatment goals with periodic re-assessment, titration of medications to objective parameters such as sedation scales and peripheral nerve stimulation, use of intermittent therapy when feasible, implementation of drug interruption strategies, and discontinuation of medications at the earliest possible time. It is important to recognize that patients evolve from severe ARDS through phases of recovery to the resolution of respiratory failure and that ventilatory management, as well as sedative and related medication requirements, will vary markedly over the course of this process.

Conclusions: A multidisciplinary, structured approach that is based on the considerations described should help achieve optimal results in this challenging patient population. (Crit Care Med 2005; 33[Suppl.]:S209–S216)

Key Words: high-frequency oscillatory ventilation; sedation; analgesia; neuromuscular blocking agents; protocols; scales

A constant principle in the management of critically ill patients is the provision of safety and comfort (1). Achieving these goals requires clinician awareness of the numerous conditions that can contribute to patient distress or interfere with effective patient care (2). These conditions include underlying medical conditions, acute medical or surgical illness, mechanical ventilation, invasive medical and nursing interventions, medications that contribute to delirium, hospital-acquired illness, and intensive care unit (ICU) environmental influences (2). Comprehensive management includes modification of these underlying causes of distress and pharmacologic and non-pharmacologic measures to optimize comfort and enhance tolerance of the ICU environment (2, 3). Conditions such as acute respiratory distress syndrome (ARDS) present particular challenges in sedation management and may require use of neuromuscular blocking agents (NMBA) for effective mechanical ventilation and oxygenation (4), particularly during use of strategies such as high-frequency oscillatory ventilation (HFOV).

FREQUENCY OF SEDATIVE, ANALGESIC, AND NMBA USE IN MECHANICAL VENTILATION, ARDS, AND HFOV

Sedation and Analgesia

Facilitation of mechanical ventilation is among the most commonly cited indications for sedative and analgesic medications, and surveys indicate their use in the majority of mechanically ventilated patients (5–10). In an international, prospective, observational study (11), 68% of 5,183 mechanically ventilated patients received sedative medications during ventilatory support (12). However, only 4.5% of patients in this study had ARDS, a condition that often requires high-intensity ventilatory support, listed as the cause of acute respiratory failure (11). A subsequent analysis of data from the ARDS Network trial of low—vs. high–tidal volume ventilation for ARDS (13) revealed that sedative medications were utilized in over 90% of patients during the first several days of mechanical ventilation (14). Approximately 80% and 75% of patients continued to require sedative medications on day 7 and day 14, respectively, with no significant difference in sedative administration between the two treatment groups based on size of tidal volume (14). Virtually all patients treated with HFOV reported in recent clinical trials and case series received sedative medications by continuous infusion to facilitate mechanical ventilation (15–17).

Neuromuscular Blockade Use

The most commonly cited indication for administering NMBA is to facilitate mechanical ventilation (18). In contrast to the widespread use of sedative medications, administration of NMBA is infrequent for mechanically ventilated patients, even including patients with ARDS. Only 9% of 5,183 consecutive mechanically ventilated adults from the previously mentioned international study (11) received NMBA during mechanical ventilation (19). Twenty-five percent of 902 ARDS patients were receiving NMBA at the time of enrollment into the ARDS Network low—vs. high–tidal volume trial (13), and 10–15% of patients continued to receive NMBA as far out as 14 days of mechanical ventilation (14).

The published experience from clinical trials and recent case series suggests...
that NMBAs have been routinely utilized for the vast majority of patients treated with HFOV (15–17). Specifically, in a series of 156 adult patients treated with HFOV at three ICUs since 1998, 90% of patients received NMBAs by continuous infusion (17). In the recent multicenter, controlled clinical trial, NMBAs were administered to all patients randomized to HFOV (15). The higher rate of NMA utilization with HFOV may be related in part to the marked severity of ARDS, when compared with other ARDS populations. However, it is more likely that a ventilatory strategy in which spontaneous ventilation can be disruptive to gas exchange, such as HFOV, will require deep sedation or chemical paralysis. This is in contradistinction to ventilatory modes, like airway pressure-release ventilation, in which spontaneous ventilation is encouraged and deep sedation and paralysis may be avoided (20). Recent expert recommendations now emphasize that not all patients require NMBAs during HFOV and that attempts should be made to avoid NMBAs altogether or limit treatment to intermittent boluses (21).

SEDATION, ANALGESIA, AND NEUROMUSCULAR BLOCKADE MANAGEMENT STRATEGIES

The use of sedative agents and NMBAs is associated with longer duration of mechanical ventilation and longer ICU length of stay (12, 19, 22). This is not unexpected and may be related primarily to higher severity of illness. However, there is evidence that strategies for effective and targeted sedation management can achieve important outcomes such as reduced duration of mechanical ventilation, lower prevalence of tracheostomy, shorter ICU length of stay, reduced drug utilization, and reduced costs (23–26). Guidelines for the management of sedation, analgesia, and neuromuscular blockade in mechanical ventilation have been published (2, 3, 18, 27, 28), and common themes include multidisciplinary structured management, drug titration to objectively measured endpoints, individualized drug selection, strategies to use the lowest effective dose and avoid drug accumulation, and avoidance of adverse effects.

Challenges of ARDS and HFOV

Sedation and analgesia management for patients with ARDS is particularly challenging because these patients generally have a long duration of mechanical ventilation, often have concomitant non-pulmonary organ dysfunction that may influence drug metabolism, require deep sedation to achieve patient-ventilatory synchrony, and have serious consequences of inadequate synchrony such as prolonged oxygen desaturation or barotrauma. During HFOV, the consequences of uncontrolled spontaneous respiration may be even more significant because a strong inspiratory effort by some patients can cause a reduction in airway pressure below the preset lower limit, which is interpreted by the ventilator as a circuit disconnection, and oscillation is terminated (17). In addition, although spontaneous breathing during HFOV may be comfortable for the patient, such breaths are not augmented—contrasting with most conventional ventilatory modes (20).

Mechanical ventilatory needs, and therefore sedative and NMA needs, vary markedly over the course of ARDS, from initial stabilization of severe gas exchange impairment to recovery. Accordingly, there are a number of transition points of management, such as from neuromuscular blockade plus sedation to sedation alone, as the patient progresses from phase to phase (Fig. 1). These phases and management transitions each require structured approaches, adding to the complexity of management. Further, mechanical ventilation and sedation management are often intertwined. For example, mental status is an important determinant of successful weaning from mechanical ventilation (29), and direct measures of mental status (29–31) or of sedation therapy (32) are incorporated into many weaning protocols.

Key Components of Sedation Management Strategies

Common themes for management of sedative and analgesic medications are outlined in Table 1. Development of guidelines or management protocols must be multidisciplinary, including physicians, nurses, and respiratory therapists who will play key roles in managing these patients. Successful implementation will require establishing “buy-in” from individuals involved in patient care and from managers of involved units. Sustainability requires continual attention to the process.

Patient Evaluation. Many patients have conditions that contribute to the development of pain, anxiety, and delirium—which are key components of patient distress (2). Patient evaluation should focus on detecting and then eliminating or controlling these factors when possible. In addition, detection and quantification of pain should be specifically sought using a pain scale (3, 33). Use of deep sedation or neuromuscular blockade, or both, makes conventional assessment difficult, and reliance on observation of pain-related behaviors such as facial grimacing or unexplained tachycardia or hypertension becomes necessary, recognizing the lack of specificity of these observations (3, 34). Use of intermittent therapy (24) or scheduled interruption of therapy (23) allows additional opportunities for detection of pain.

Figure 1. Schematic representation of the progression of the stage of management, stage of mechanical ventilation, and stage of sedative and neuromuscular blockade therapy over the course of time in severe acute respiratory distress syndrome. Note the transitions, for example, from conventional ventilation to high-frequency oscillatory ventilation (HFOV) or from deep sedation to moderate sedation.

<table>
<thead>
<tr>
<th>Stabilization</th>
<th>Maintenance</th>
<th>De-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Ventilation</td>
<td>HFOV</td>
<td>Conventional Ventilation</td>
</tr>
<tr>
<td>Deep sedation + Neuromuscular blockade</td>
<td>Deep sedation</td>
<td>Moderate sedation</td>
</tr>
</tbody>
</table>

S210 Crit Care Med 2005 Vol. 33, No. 3 (Suppl.)
Table 1. Important components of treatment guidelines for sedation, analgesia, and neuromuscular blockade in patients with acute respiratory distress syndrome

1. Perform patient assessment: evaluate for treatable factors contributing to pain, anxiety, delirium, and patient-ventilator dysynchrony; optimize patient comfort
2. Select sedative, analgesic, or neuromuscular blocking agent (NMBa) drugs based on clinical characteristics, risk of adverse effects, and cost
   a. Sedatives
      i. If rapid onset of action desired, select midazolam
      ii. If rapid emergence desired, select propofol
      iii. If renal insufficiency is present, avoid midazolam
      iv. If hemodynamic instability is present, avoid propofol
      v. If duration of >48 hrs, avoid propofol
   b. Analgesics
      i. If rapid onset of action desired, select fentanyl
      ii. If renal insufficiency is present, avoid morphine
      iii. If hemodynamic instability is present, avoid morphine
      iv. For intermittent therapy, select morphine or hydromorphone
   c. NMBAs
      i. If renal insufficiency or liver dysfunction is present, select atracurium or cisatracurium
      ii. If tachycardia or hypertension are unacceptable, avoid pancuronium
      iii. If intermittent dosing acceptable, select pancuronium (or vecuronium)
3. Establish treatment goals for sedative, analgesic, and NMBa medications
   a. Comfortable and free of distress
   b. Satisfactory patient-ventilator synchrony
   c. Apnea
   d. Complete muscle relaxation
4. Utilize objective measures of sedation, analgesia, or neuromuscular blockade
   a. Sedation and analgesia
      i. Sedation scale: document at least every 4 hrs
      ii. Consider Bispectral index monitoring if neuromuscular blockade is in use
      iii. Pain scale
   b. Neuromuscular blockade
      i. Clinical evaluation
      ii. Train-of-four peripheral nerve stimulator monitoring—every 4 hrs (especially for vecuronium infusion or deep paralysis)
5. Titrate medications to achieve effectiveness based on treatment goals and safety using objective measures to avoid overdosage. Attempt to use the lowest effective dose, utilizing intermittent therapy or scheduled drug interruption, as tolerated
   a. Establish target (sedation scale, train-of-four, etc) and frequently adjust dosage to achieve target, using lowest effective dose
   b. Use intermittent sedative, analgesic, and NMBa therapy if feasible
   c. If continuous infusion therapy, use daily interruption of medications (sedatives/analgesics, NMBAs)
6. Take steps to avoid adverse effects of treatment

**Goals of Sedation Therapy and Sedation Evaluation.** The goals of treatment with sedative and analgesic medications should be explicitly established for each patient, communicated within the ICU team, and reexamined at least daily. Provision of comfort and relief of distress is always one of the goals; however, in ARDS, and particularly with HFOV management, patient-ventilator synchrony or apnea may be the target. In goal-directed sedation and analgesia, the use of a validated sedation scale is useful (2, 3). Desirable features of a sedation scale include: a) multidisciplinary development, b) ease of use, recall and interpretation, c) well-defined discrete criteria for each level, d) sufficient sedation levels for titration of sedative and analgesic medications, e) an assessment of agitation, and f) rigorous testing of reliability and validity in relevant patient populations (35). There are many scales (36, 37); however, sedation scales that have been tested for validity and reliability in adult patients include the Ramsay sedation scale (38), the sedation agitation scale (39), the motor activity assessment scale (40), the Vancouver interaction and calmness scale (41), the Richmond agitation-sedation scale (42), the adaptation to the intensive care environment instrument (43), and the Minnesota sedation assessment tool (44). The arousal components of recently developed scales, such as the Richmond agitation-sedation scale, the adaptation to the intensive care environment instrument, the Minnesota sedation assessment tool, and the Ramsay sedation scale, rely on direct observation of simple responses (i.e., eye opening, movement) to progressively intense stimuli (the tester’s voice, then physical stimulation), yielding multiple discrete levels of arousal/sedation that are suitable for titrating sedative medications (38, 42–44). The Richmond agitation-sedation scale also incorporates levels of agitation and a measure of cognition within a single scale, which can all be assessed in 30 secs (42). The adaptation to the intensive care environment is unique among the sedation assessment tools in that patient tolerance of the ICU environment is also addressed, although approximately 20 steps are needed to assess all five subscales (43). Use of a sedation scale can help reduce the frequency of oversedation (45) and has been incorporated into successful protocols (23, 24, 26, 30).

Assessment of the level of sedation is more complicated when an NMBa is added because the patient responses that are examined in sedation scales may be masked by muscle paralysis. Unexplained tearing, tachycardia, or hypertension may raise suspicions that sedation and analgesia is insufficient; however, these are nonspecific findings (34). Most helpful is the use of intermittent bolus NMBa therapy or scheduled NMBa withdrawal that provides paralysis-free periods for sedation scale testing and assessment of pain. The employment of a device, such as the Bispectral index, that converts electroencephalographic signals into a digital scale from 100 (fully alert) to 0 (isoelectric electroencephalogram) with continuous
rapid onset of action but a more variable awakening time. Midazolam is metabolized in the liver by oxidation, yielding an active metabolite, alpha-hydroxymidazolam, which is excreted by the kidney. Patients with renal insufficiency may have markedly prolonged sedation (61), and we avoid using midazolam in these patients (2). Some experts recommend against using midazolam beyond 24 hrs of sedation (3) because of concerns about prolonged and variable recovery compared with lorazepam (62). However, other studies demonstrate 2- to 3-fold shorter recovery times with midazolam compared with lorazepam (63). Lorazepam has a more gradual onset of action and is metabolized in the liver by glucuronidation to inactive metabolites with an intermediate duration half-life. Very high-dose and prolonged infusions have been associated with a syndrome of hyperperosmolality, lactic acidosis, and reversible renal insufficiency (64). The implementation of a protocol that focused on increased utilization of lorazepam was associated with lower costs without prolonging weaning (65). Although lorazepam is recommended for long-term sedation (3, 66), a 1998 survey indicated that midazolam and propofol are frequently used for >24 hrs (10). Interestingly, in a survey of 647 European ICU physicians, midazolam was used often or always by 63% of respondents, and propofol was used by 35% (67).

Fentanyl, morphine, and hydromorphone are the most widely used analgesics for ICU patients by bolus or continuous intravenous delivery, and there is no routinely preferred agent for long-term analgesia (3, 28). Fentanyl has a rapid onset of action and the shortest half-life, but repeated dosing may cause accumulation (3). Morphine has slower onset and longer duration of action. It is metabolized by glucuronidation to a number of compounds, including morphine-6-glucuronide, which is more potent than the parent compound and accumulates in renal insufficiency (68). Morphine is associated with histamine-related hypotension. We avoid administering morphine to patients with hemodynamic instability or renal insufficiency (2). Hydromorphone has an intermediate duration of action, is metabolized by glucuronidation, and has no active metabolites. It is not associated with histamine release. Surveys indicate that morphine and fentanyl are used most widely (10, 67).

Sedation and Analgesia Protocols. Strategies to optimally utilize sedative and analgesic medications for mechanically ventilated patients include proper drug selection based on patient characteristics, titration to specific end points using a sedation scale and goals of therapy, and utilizing protocols to avoid accumulation of drugs through use of intermittent therapy or scheduled cessation of medications. Several groups of investigators have introduced sedation protocols with varying levels of success. After implementing a sedation scoring system and sedation protocol, Brattebo et al. (26) were able to reduce duration of mechanical ventilation and ICU length of stay. Mascia et al. (25) developed and implemented a protocol for sedation, analgesia, and neuromuscular blockade for mechanically ventilated ICU patients. Compared with the baseline period, protocol patients had lower drug costs, ventilator time, and ICU length of stay. Impressively, the use of NMBAs declined from 30% of patients to 5%. MacLaren et al. (69) implemented an evidence-based sedation and analgesia protocol, with a high protocol adherence rate, and noted mixed results when compared with the pre-protocol period. Patients experienced less pain and discomfort and had lower hourly cost of sedation, probably due to increased lorazepam use. However, duration of sedation use and ventilator weaning were each about 24 hrs longer with the new protocol, offsetting the drug-related cost savings. Kollef et al. (22) observed that continuous intravenous sedation and analgesia was associated with longer duration of mechanical ventilation after adjusting for numerous co-variables. This observation led to a prospective trial at the same institution that compared nurse-led protocol-based management with traditional management (24). This strategy emphasized conversion from continuous to intermittent therapy using primarily lorazepam and fentanyl. The protocol patients had significantly shorter duration of mechanical ventilation, shorter ICU and hospital length of stays, and one half the tracheostomy rate of nonprotocol patients. It is noteworthy that the protocol is complex and that the frequent dosing of intermittent therapy (as frequent as every 2 hrs before continuous infusion is initiated) might not be embraced by all nurses.

Kress et al. (23) tested scheduled daily interruption of sedative and analgesic continuous intravenous infusions. In this

S212 Crit Care Med 2005 Vol. 33, No. 3 (Suppl.)
The daily interruption protocol was associated with a significant reduction in duration of mechanical ventilation, shorter ICU length of stay, and fewer diagnostic studies to assess altered mental status. There was no increase in serious agitation such as self-removal of important tubes and catheters. Subsequent post hoc analysis of the study population showed the daily interruption strategy was associated with fewer ICU-related complications (70). Concerns that the shock of daily withdrawal of all sedative and analgesic medications might predispose the patient to postranspiratory distress disorder (71) were quelled when the same investigators demonstrated strong trends for fewer postranspiratory distress disorder symptoms and less psychological stress than with conventional management (72). Patients in the original study (23) were also randomized to midazolam or propofol (both groups also received morphine). Interestingly, daily interruption of midazolam and morphine resulted in lower total doses compared with conventional care, yet there was no difference in the total propofol or morphine with daily interruption in the propofol-infused patients. Thus, the shorter duration of mechanical ventilation is likely related to less drug accumulation among the midazolam-treated patients yet cannot explain the benefit observed in the propofol-infusion patients. It may be that the daily awakening event provides an opportunity for ventilator weaning to be contemplated at an earlier time than those without daily sedation interruption (73).

Extrapolation of these findings to HFOV-managed ARDS patients should be with caution because the consequences of sedation withdrawal with resulting patient-ventilator dysynchrony may be more serious (21). Approximately 25% of patients in the daily interruption clinical trial (23) had ARDS and 12% were receiving NMBAs, although none were receiving HFOV. Application of a daily interruption strategy or intermittent therapy protocol during the conventional ventilation phase of patient management seems logical. Clinical judgment must be exercised during HFOV as to the safety of approaches that promote an awake or agitated state. It may be that a modified approach whereby partial awakening is achieved, perhaps by targeting a lighter sedation level, will safely reduce drug accumulation and present an opportunity for reducing ventilatory support.

Neuromuscular Blockade

Similar to sedation and analgesia, management of neuromuscular blockade requires patient-based drug selection, identification of goals of therapy and monitoring for safety and effectiveness, and titration of drugs to the lowest effective dose for the shortest possible duration using intermittent therapy or daily drug interruption (18, 27, 74).

NMBAs. Among the various NMBAs, pancuronium, vecuronium, atracurium, and cis-atracurium are used most often for ICU management of severe respiratory failure. Pancuronium is an amino-steroid agent with intermediate duration of action such that intermittent dosing is feasible. Primary limiting characteristics include vasolytic and sympathomimetic properties that can result in tachycardia and hypertension. In addition, like vecuronium, it is metabolized to active compounds that accumulate in the setting of renal insufficiency. Vecuronium, also an amino-steroid, has a shorter duration of action and thus is used primarily via continuous infusion. Atracurium is an intermediate acting benzylisoquinolinium that is eliminated through Hofmann degradation, which is independent of organ function. Atracurium promotes histamine release that can lead to bronchospasm or hypotension. Cisatracurium is an isomer of atracurium with reduced histamine releasing properties. Atracurium and cisatracurium have faster and more predictable recovery profiles than vecuronium (75–77). Accordingly, if renal insufficiency or liver dysfunction is present, atracurium or cisatracurium should be selected. Otherwise, if intermittent therapy is desired, pancuronium is used unless tachycardia or hypertension would be poorly tolerated, in which case, vecuronium, atracurium, or cisatracurium would be preferred (18, 27, 74).

Goals and Monitoring of Neuromuscular Blockade. The clinical goal of neuromuscular blockade is to follow the investigator on request, 3) squeeze a hand on request, or 4) stick out the tongue on request, at which time the insuffusions are restarted at one half the dose. The daily interruption protocol was associated with a significant reduction in duration of mechanical ventilation, shorter ICU length of stay, and fewer diagnostic studies to assess altered mental status. There was no increase in serious agitation such as self-removal of important tubes and catheters. Subsequent post hoc analysis of the study population showed the daily interruption strategy was associated with fewer ICU-related complications (70). Concerns that the shock of daily withdrawal of all sedative and analgesic medications might predispose the patient to postranspiratory distress disorder (71) were quelled when the same investigators demonstrated strong trends for fewer postranspiratory distress disorder symptoms and less psychological stress than with conventional management (72). Patients in the original study (23) were also randomized to midazolam or propofol (both groups also received morphine). Interestingly, daily interruption of midazolam and morphine resulted in lower total doses compared with conventional care, yet there was no difference in the total propofol or morphine with daily interruption in the propofol-infused patients. Thus, the shorter duration of mechanical ventilation is likely related to less drug accumulation among the midazolam-treated patients yet cannot explain the benefit observed in the propofol-infusion patients. It may be that the daily awakening event provides an opportunity for ventilator weaning to be contemplated at an earlier time than those without daily sedation interruption (73).

Extrapolation of these findings to HFOV-managed ARDS patients should be with caution because the consequences of sedation withdrawal with resulting patient-ventilator dysynchrony may be more serious (21). Approximately 25% of patients in the daily interruption clinical trial (23) had ARDS and 12% were receiving NMBAs, although none were receiving HFOV. Application of a daily interruption strategy or intermittent therapy protocol during the conventional ventilation phase of patient management seems logical. Clinical judgment must be exercised during HFOV as to the safety of approaches that promote an awake or agitated state. It may be that a modified approach whereby partial awakening is achieved, perhaps by targeting a lighter sedation level, will safely reduce drug accumulation and present an opportunity for reducing ventilatory support.

Neuromuscular Blockade

Similar to sedation and analgesia, management of neuromuscular blockade requires patient-based drug selection, identification of goals of therapy and monitoring for safety and effectiveness, and titration of drugs to the lowest effective dose for the shortest possible duration using intermittent therapy or daily drug interruption (18, 27, 74).

NMBAs. Among the various NMBAs, pancuronium, vecuronium, atracurium, and cis-atracurium are used most often for ICU management of severe respiratory failure. Pancuronium is an amino-steroid agent with intermediate duration of action such that intermittent dosing is feasible. Primary limiting characteristics include vasolytic and sympathomimetic properties that can result in tachycardia and hypertension. In addition, like vecuronium, it is metabolized to active compounds that accumulate in the setting of renal insufficiency. Vecuronium, also an amino-steroid, has a shorter duration of action and thus is used primarily via continuous infusion. Atracurium is an intermediate acting benzylisoquinolinium that is eliminated through Hofmann degradation, which is independent of organ function. Atracurium promotes histamine release that can lead to bronchospasm or hypotension. Cisatracurium is an isomer of atracurium with reduced histamine releasing properties. Atracurium and cisatracurium have faster and more predictable recovery profiles than vecuronium (75–77). Accordingly, if renal insufficiency or liver dysfunction is present, atracurium or cisatracurium should be selected. Otherwise, if intermittent therapy is desired, pancuronium is used unless tachycardia or hypertension would be poorly tolerated, in which case, vecuronium, atracurium, or cisatracurium would be preferred (18, 27, 74).

Goals and Monitoring of Neuromuscular Blockade. The clinical goal of neuromuscular blockade is to follow the investigator on request, 3) squeeze a hand on request, or 4) stick out the tongue on request, at which time the insuffusions are restarted at one half the dose. The daily interruption protocol was associated with a significant reduction in duration of mechanical ventilation, shorter ICU length of stay, and fewer diagnostic studies to assess altered mental status. There was no increase in serious agitation such as self-removal of important tubes and catheters. Subsequent post hoc analysis of the study population showed the daily interruption strategy was associated with fewer ICU-related complications (70). Concerns that the shock of daily withdrawal of all sedative and analgesic medications might predispose the patient to postranspiratory distress disorder (71) were quelled when the same investigators demonstrated strong trends for fewer postranspiratory distress disorder symptoms and less psychological stress than with conventional management (72). Patients in the original study (23) were also randomized to midazolam or propofol (both groups also received morphine). Interestingly, daily interruption of midazolam and morphine resulted in lower total doses compared with conventional care, yet there was no difference in the total propofol or morphine with daily interruption in the propofol-infused patients. Thus, the shorter duration of mechanical ventilation is likely related to less drug accumulation among the midazolam-treated patients yet cannot explain the benefit observed in the propofol-infusion patients. It may be that the daily awakening event provides an opportunity for ventilator weaning to be contemplated at an earlier time than those without daily sedation interruption (73).

Extrapolation of these findings to HFOV-managed ARDS patients should be with caution because the consequences of sedation withdrawal with resulting patient-ventilator dysynchrony may be more serious (21). Approximately 25% of patients in the daily interruption clinical trial (23) had ARDS and 12% were receiving NMBAs, although none were receiving HFOV. Application of a daily interruption strategy or intermittent therapy protocol during the conventional ventilation phase of patient management seems logical. Clinical judgment must be exercised during HFOV as to the safety of approaches that promote an awake or agitated state. It may be that a modified approach whereby partial awakening is achieved, perhaps by targeting a lighter sedation level, will safely reduce drug accumulation and present an opportunity for reducing ventilatory support.
greatest benefit from scheduled train-of-four testing (74).

ICU-Acquired Myopathy. Although prolonged neuromuscular blockade is important, ICU-acquired myopathy is a more serious NMBA-related cause of weakness in the ICU (86) because of the delayed recovery that can require weeks of rehabilitation (87). ICU-acquired myopathy, also known as acute quadriplegic myopathy syndrome, among other terms, is most commonly associated with concomitant prolonged corticosteroid administration and is likely due to a combination of myonecrosis (88) and reduced myosin production (89). Unfortunately, ICU-acquired myopathy occurs despite conscientious avoidance of drug overdose by train-of-four monitoring. Originally described with amino-steroid agents, it has subsequently been described with all NMBAs, although the relative frequency among agents is not known (83, 90, 91).

Selected patients with severe ARDS and HFOV management may require continuous neuromuscular blockade; however, considerable effort should be made to limit the duration of NMBA administration, particularly if corticosteroids are given concomitantly. In addition, although not well studied, the concept of a daily interruption of therapy or the use of intermittent therapy a) helps avoid unnecessary drug accumulation, b) allows periodic evaluation of neurologic status, c) permits assessment of sedation and analgesic needs, and d) promotes periodic reassessment of the need for further neuromuscular blockade (74). An important factor, individualized for each patient and changing over time, is the tolerance of temporary cessation of paralysis.

CONCLUSIONS

A principle goal of implementation of protocols and guidelines is to consistently apply well-reasoned strategies to achieve more effective and streamlined patient care across multiple care providers. Simpler protocols often work better. However, ventilatory and sedative management of respiratory failure in severe ARDS is complex, in part because of the phases of illness and recovery that patients will proceed through. The concepts discussed in this and other reviews should aid in implementing successful strategies.

REFERENCES


83. Segredo V, Caldwell JE, Matthay MA, et al:


