Management of the agitated intensive care unit patient

INTRODUCTION: AGITATION ROUNDTABLE MEETING OVERVIEW

Agitation: 1. Violent motion. 2. Strong or tumultuous emotion.

Management of the agitated patient is fast becoming an area of major breakthroughs for critical care medicine. To illustrate, Figure 1 shows the total number of articles found on MEDLINE using a combination of search words related to sedation and critical care. This crude survey demonstrates an exponential rise in activity surrounding this topic and helps support the view that study of agitation in the critically ill patient is of rapidly expanding importance. Moreover, management of the agitated patient has developed into an economically powerful subject, both for pharmaceutical companies and for caregivers interested in improving the efficient use of intensive care unit (ICU) resources. It is increasingly apparent that outcomes are significantly influenced by the manner in which agitation is managed.

The quantity of articles being published is only part of the picture. Investigations related to agitation in critical care are yielding a variety of intriguing observations including post-traumatic stress disorder and post-ICU depression, diagnosis of delirium, objective monitoring technology, sleep pattern changes, process/management strategies to enhance clinical and economic outcomes, scoring systems, tailorability of therapeutic approaches, and bronchodilatory, antioxidant, and immunosuppressive properties of sedative agents.

Rather than simply discussing strategies for sedation, it is the deliberate intent of this continuing education program to focus on the specific topic of agitation (in the ICU patient). It is noteworthy that, although it is one of the most common issues facing critical care practitioners, agitation in the ICU has no clear and concise definition.

The simple definition stated at the beginning of this article is from Funk and Wagnall's 1982. This explanation of "agitation" has merit because it encompasses both physical and emotional distress. Under this characterization, either the nonsedated paralyzed patient or the comatose patient with patient-ventilator asynchrony can be considered agitated, even though the two may represent opposite ends of a spectrum.

Accurate diagnosis of the cause of agitation frequently requires a careful analysis of the patient's history and physical examination, review of laboratory and other diagnostic data, knowledge of the effectiveness of concomitant therapies, collaboration among members of the team and family, and a good deal of experience. The cause of agitation is often multifactorial (e.g., pain and confusion or delirium and withdrawal), and even with successful management it is difficult to be certain about precipitating factors in any single case. Anecdotes from patients and clinicians can serve as powerful tools for the critical care team's armamentarium and help increase understanding from both sympathetic and empathetic perspectives.

Pharmacologic management strategies for agitation include both prevention and treatment. Prevention commonly guides the hand of the critical care clinician when a patient is being stabilized and drips are ordered for analgesia and sedation in anticipation of agitation. Fine-tuning the therapy using agitation scales, daily awakening, and other strategies take on more of a treatment quality, as do *pro re nata* (PRN) agitation orders. Nonpharmacological approaches include a variety of environmental adjustments that are frequently underutilized.

Yet, as obvious as these concepts for definition, diagnosis, and management may seem, it is difficult to consistently apply them to the literature (with the exception of short-term usage). There are a number of well-designed and well-executed studies in longer-duration agitation management but, excluding those in very focused populations (e.g., neurologic injury), most studies lump patients into groups for the purpose of assessing differing sedative regimens.

Comparative pharmaceutical trials have been extraordinarily important to clinicians who deal regularly with agitation. These studies, as well as trials using innovative management techniques, are becoming increasingly sophisticated in the area of pharmacoeconomic assessment. There is still, however, a paucity of comprehensive studies evaluating the integration of economic, clinical, and humanistic outcomes of agitated ICU patients. Existing economic analyses include variables such as drug acquisition costs, ventilator duration, and ICU length of stay (LOS) to determine the "cost effectiveness" of one drug regimen over another; these are often only partial in their scope. Assigning or assuming costs for time in ICU or on a ventilator is fraught with the problems of evaluating the fixed and variable components. Opportunity costs are usually ignored, as they are exceedingly difficult to determine. And, failure to include post-ICU cost and outcome information ignores the post-ICU morbidity that appears linked to ICU sedation usage. These types of problems with economic analyses are widespread in the critically ill population and are not unique to the topic of agitation management. Notwithstanding, it can be said with a reasonable degree of confidence that the drug acquisition cost of various regimens is only one—often small—piece of the larger economic puzzle.

Given the current tide of activity, it is conceivable that the approach to managing agitation in the critically ill patient will rise (or is rising) to a new level of sophistication. At this new level, pharmacologic and nonpharmacologic approaches will be highly selective and fine-tuned to more precisely address the

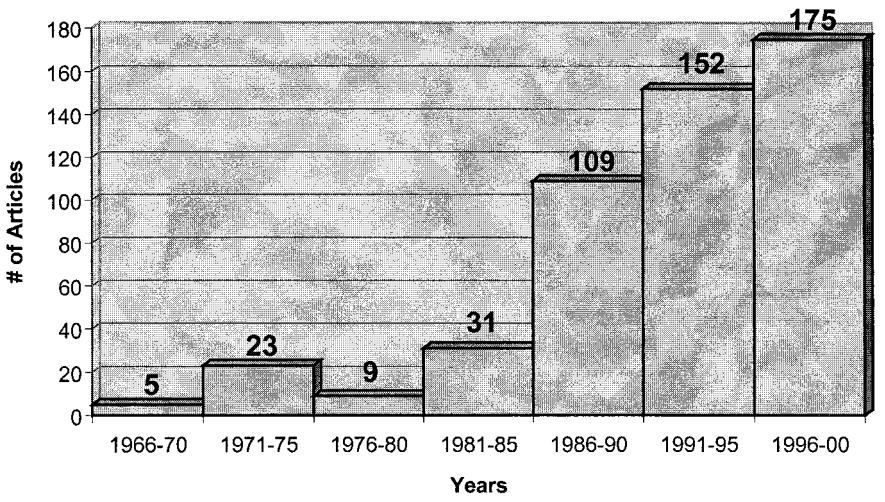

Figure 1. Number of articles on sedation in the intensive care unit.

psychophysiologic disturbances found in each critically ill individual. As a result, the critically ill population will experience fewer side effects, shorter ICU courses, better short-term and long-term outcomes, improved cost-effectiveness of care, and reduced morbidity.

The fishbone/cause-and-effect diagram displayed in Figure 2 was designed to illustrate the challenge of managing agitation in the ICU patient by demonstrating schematically the interrelationship of many of the points presented in this piece. Each item can be a significant factor, and changing just one (e.g., unilaterally starting a protocol) rarely works unless careful thought is given to all the other variables. The cause-and-effect diagram is a quality improvement tool that assists in identifying those variables.

The authors of this supplement are an experienced, multidisciplinary group of clinicians who discuss the topic of agitation from an academic and clinical perspective spanning the development of modern critical care. The primary intention of this continuing education program is to provide a practical framework for managing agitation. It is hoped that the areas of controversy will be stimulating to the reader. Two overriding questions should emerge: What kind of evidence is needed to advance the management of agitation in the ICU? And, how do we bridge the evidence-care gap and put existing and emerging evidence into consistent daily practice?

Program Background

In June 2001, the authors participated in a tele-roundtable meeting. Each author presented his or her topic in depth followed by a brief question-and-answer period. At the end of the formal presentations, a series of questions was presented and the roundtable discussion ensued. The questions, which were prepared in advance but not made available to the authors until the time of the conference, were meant to create controversy and offer brainstorming ideas outside the structure demanded by scientific writing.

While finalizing their first drafts, the authors were provided a draft of the revised *Clinical Practice Guidelines* for the sustained use of sedatives and analgesics, which is also published in this month's issue of *Critical Care Medicine*. It is important to stress that this supplement is not meant to supplant any of the recommendations laid out by the Guideline Development Task Force. Opinions expressed in this program may differ when the grade of evidence is lower, however; this group made no attempt to identify an evidence-based grade. Moreover, this continuing medical education activity does not limit its scope with respect to duration of sedative use. Finally, this work is meant to be more speculative in its span.

Selectively, a number of topics were not discussed in detail; these include shock and sepsis. Although managing agitation in sepsis and shock is an essential part of care, it was felt that only generalities could be addressed using the fundamentals provided in the following sections. Notwithstanding, observations of differing effects of sedating agents on free radicals and the immune system, for example, might lead to interesting breakthroughs in agitation management for critically ill patients.

PHYSIOLOGY, PATHOPHYSIOLOGY, AND DIFFERENTIAL DIAGNOSIS OF ICU AGITATION

Agitation frequently occurs in critically ill adult patients in the ICU and is associated with potentially dangerous complications such as self-extubation, removal of arterial and venous catheters, increased systemic and myocardial oxygen consumption, and failure to participate in therapeutic interventions (1, 2). The agitation syndrome may be caused by many factors, including the underlying illness itself, discomfort associated with invasive catheters and tubes, and the many stimuli common to the ICU environment. Agitation develops regardless of age, sex, or underlying diseases. The syndrome complicates management in the ICU, often leading to further morbidity and complications.

Definition, Symptoms, and Signs of Agitation

Although a simple definition of agitation in the critically ill patient is difficult to find, agitation can be described in several ways. Agitated patients exhibit continual movement, characterized by constant fidgeting, moving from side to side, pulling at dressings and bed sheets, and attempting to remove catheters or other tubes. The agitated patient remains disoriented in one of several spheres. There may be a total lack of awareness as to name, place, or time. Alternatively, patients may know who they are, but have no idea of their current location. Depending on the degree of agitation and the ability of the patient to listen or communicate, commands may or may not be successfully followed (4). The more complicated the request, the less likely the patient will be able to respond in an appropriate manner. Patients capable of communicating may exhibit intermittent, irrational thoughts or sentences. Within a long string of rambling conversation, some statements may make sense but the vast majority of the conversation remains unintelligible (5). Shouting, calling out, or moaning can add to the clinical presentation. The agitated patient will often exaggerate complaints of pain, when, in actuality, other factors such as

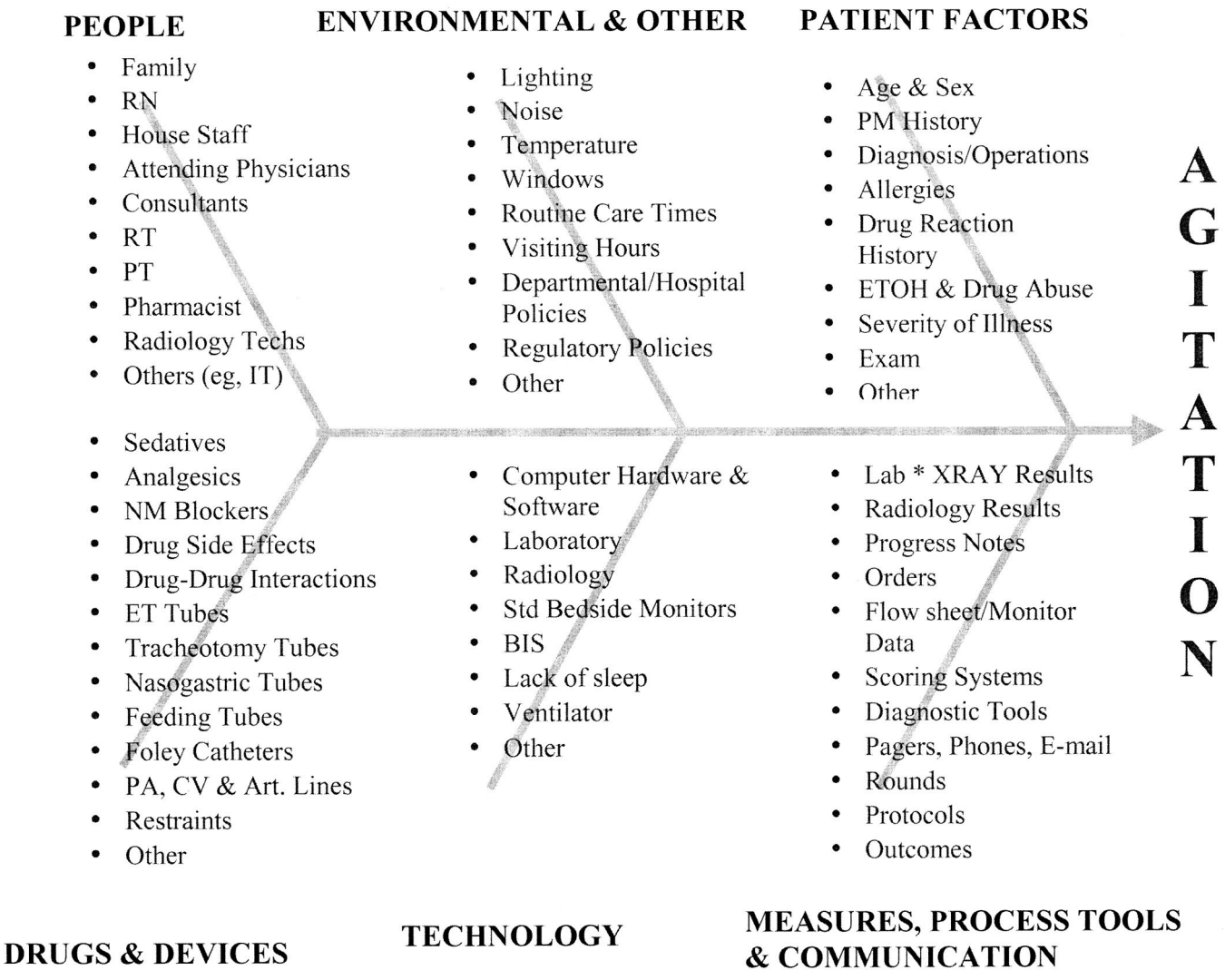

Figure 2. Fishbone diagram of factors that may impact agitation.

the need to urinate or have a bowel movement are the causes of the complaints.

It is important to note that none of the above descriptions characterize a patient undergoing neuromuscular blockade who is agitated because of lack of sedation and analgesia. This condition, which often results in patients having vivid recall while under pharmacologic paralysis, is a particularly disturbing occurrence to critical care unit personnel, and may have long-term negative effects on the patient.

Vital signs are generally abnormal in the agitated patient. Blood pressure may increase to dangerously high ranges, respiratory rate may be elevated, and heart rate may increase, with potential for ischemia (6). An elevated metabolic rate results in an increase in overall oxygen requirements and, if left to continue for a protracted period of time, an increase in caloric demand. The agitated patient with a rapid respiratory rate may not be able to synchronize respirations with the mechanical ventilator, resulting in high airway pressures, inadequate ventilation, and decreases in Po_2 with either increases or decreases in Pco_2, all of which further propagate the tendency toward agitation. These physiologic changes frequently vary over 24 hrs depending on the chronicity or intermittency of the agitation. Agitated patients generally cannot concentrate or pay attention to the caregivers around them, making the ability to follow requests or demands exceedingly difficult.

Etiological Factors Contributing to Agitation

In the postoperative patient, the multiple pharmacologic agents typically administered during the perioperative stage can result in significant and often unpredictable interactions, leading to agitation and confusion. These agents include benzodiazepines, opioids, inhalation agents, anticholinergics, antibiotics, and muscle relaxants; they can interact in unpredictable ways and may lead to a difficult management situation, especially in the elderly. In addition to drug–drug interactions, some agents alone, including lorazepam and anticholinergics, have been associated with the development of agitation; once again, the aged are particularly at risk (7). Frequently, the effects of these drugs may not be related to the agent itself, but rather to multiple metabolites that have varying times of degradation and excretion (see Table 1).

A significant factor in the development of agitation in critically ill patients, predominantly in the postoperative period, is failure to provide adequate pain

Table 1. Medications associated with agitation in patients in the intensive care unit (8)

Antibiotics	Cardiac Drugs
Acyclovir	Captopril
Amphotericin B	Clonidine
Cephalosporins	Digoxin
Ciprofloxacin	Dopamine
Imipenen—cilastatin	Labetalol
Ketoconazole	Lidocaine
Metronidazole	Nifedipine
Penicillin	Nitroprusside
Rifampin	Procainamide
Trimethoprim—sulfamethoxazole	Propranolol
	Quinidine sulfate
Anticonvulsants	**Corticosteroids**
Phenobarbital	Dexamethasone
Phenytoin	Methylprednisolone
Miscellaneous Drugs	**Narcotic Analgesics**
Hydroxyzine	Codeine
Ketamine	Meperidine
Metoclopramide	Morphine sulfate
Theophylline	
Anticholinergics	
Benzodiazepines	
Nonsteroidal anti-inflammatory agents	

control (8). In the United States, inadequate pain management is often a result of opioids being dosed at suboptimal levels because of concerns of respiratory depression and/or the development of dependence (9). However, these side effects are unlikely over the short term if the medication is properly titrated to patient comfort. Consequently, as clinicians we must ensure that patients receive the appropriate dose necessary to achieve continual pain relief.

Hypoxemia has long been associated with agitation. ICUs in most hospitals have documented numerous clinical incidences in which hypoxemia had been misdiagnosed as agitation. Po_2 levels of 60 mm Hg or less (or oxygen saturations below 90%) can contribute to agitation secondary to hypoxemia. Hypotension has also been associated with agitation and is considered a form of brain injury resulting from hypoperfusion. Likewise, hyper- and especially hypoglycemia can promote severe agitation. Uremia and the presence of elevated levels of heavy metals such as lead, mercury, and manganese also have been identified as causes of significant agitation in the critically ill patient (4, 7).

Another cause of minor to severe agitation is brain injury, including closed head trauma and bleeds from a ruptured aneurysm with resulting subarachnoid hemorrhage. Thrombotic stroke may cause agitation as well. Brain abscesses, seizures, infections such as meningitis, and air embolism have all been associated with persistent and severe degrees of agitation (4, 7). A common situation involves frontal lobe injury following brain trauma, in which patients usually display increasing agitation, particularly as they begin to awaken. Although difficult to control, this increase in agitation can paradoxically be taken as a positive sign in the patient's recovery. Withdrawal from alcohol or from other agents including cocaine, opioids, and sedatives such as benzodiazepines all contribute to brain injury and agitation (10). Cigarette smokers can suffer agitation from a lack of nicotine. In many circumstances, without an adequate patient history, it may be difficult to ascribe a cause for agitation.

Agitation can occur in patients who develop significant ventilator desynchronization. This is frequently caused by a poorly performing ventilator, with a delay in responding to the patient's efforts at spontaneous breathing. Patients who require short- or long-term intubation may also develop agitation, because of the stimulus of the endotracheal tube itself. Some intubated patients who are relatively alert become frustrated by their inability to communicate and then evolve into a cycle of continued agitation. Patients frequently become anxious and therefore agitated over the seriousness of being critically ill. Finally, the ICU itself, with its high noise levels, lights, and continual other stimuli, can significantly contribute to further agitation (7, 11).

Differential Diagnosis of Agitation

Agitated patients require that the clinician undertake a detailed work-up to find and eliminate the various possible causes. At the top of any list, because of its accompanying danger, should be hypoxemia, which can be readily detected by both arterial blood gas analysis and measurement of oxygen saturation (12). Of importance are occasions when a patient with a low cardiac output state has perfusion that is too low to maintain adequate oxygenation, resulting in hypoxemia resulting from cardiac dysfunction rather than pulmonary dysfunction.

Metabolic abnormalities can usually be detected by laboratory analysis, including a basic electrolyte panel and determination of specific factors including phosphate, calcium, and glucose levels. It is often necessary to order additional tests, not routinely performed, such as a thyroid panel and liver function studies. Deficiencies in vitamin B-12, niacin, and thiamine should be considered, as well as heavy metal intoxication with lead, mercury, or manganese (4). A combination of medical history, physical findings, and appropriate laboratory testing will usually identify a metabolic aberration.

Neurologic abnormalities often require not only a detailed examination but also a computed tomography (CT) scan and, in some cases, a magnetic resonance imaging (MRI) scan. Undetected blood in the brain after a bleed from an aneurysm or hypertensive bleed can cause significant agitation and an inability to respond appropriately to stimuli. An electroencephalogram (EEG) study may be useful in the determination of diffuse encephalopathy, but is rarely specifically diagnostic. Nevertheless, in instances where patients have received significant amounts of neurodepressant drugs such as barbiturates or benzodiazepines, the EEG may be a valuable diagnostic tool. Drastically elevated blood pressure in an agitated patient should alert clinicians to a suspicion of hypertensive encephalopathy, a condition requiring immediate control of

blood pressure as well as follow-up neurologic and CT examinations to rule out an intracranial bleed.

Obvious sources of pain, such as operative procedures, are important causative factors in the development of agitation. However, other less overt causes should not be overlooked—pain from chest tubes, bladder spasm (which can develop from the placement of catheters for urinary drainage), or injuries that may have occurred at the time of trauma.

Patients with chronic pain syndromes, such as low back pain, may become quite uncomfortable when confined to one position in a hospital bed in the ICU. Obtaining an adequate history will assist in making this specific diagnosis.

Consequences of numerous drug interventions—drug reactions, drug interactions, and drug withdrawal—increase the incidence of agitation in the ICU (6). The occurrence of undesirable drug–drug interactions should always be considered when multiple drugs are being used for pain, anxiety, and other psychobiological issues. To diagnose an adverse drug interaction, it is often necessary to sequentially eliminate one or more agents, or in some cases all agents. Even then, it may take several days for the drugs and their metabolites to clear the patient's system before a positive response can be seen.

Infections can lead to agitation, but are more likely to manifest as increased lethargy, with the patient becoming less responsive to stimuli and commands. One possible cause of infection in the ICU is direct bacterial or viral contamination of the cerebrospinal fluid. Endotoxin release from an ongoing illness may directly affect brain function. It has been demonstrated in patients with sepsis that amino acid levels are commonly altered both in plasma and cerebrospinal fluid. Furthermore, normal brain metabolism can be impaired in septic patients (7). Because sepsis is frequently associated with significant vasodilatation caused by the release of nitric oxide, altered cerebral perfusion may be an important mechanism for abnormal brain metabolism. This problem must be viewed seriously, inasmuch as patients who develop septic encephalopathy appear to have twice the mortality rate of other patients.

Renal and hepatic failure may also lead to various levels of agitation and even somnolence. Diagnostic features of hepatic failure include neurologic dysfunction with signs of encephalopathy and triphasic waveforms seen on the EEG. Similar EEG changes can also be present in renal failure; however they are not necessarily specific. Although patients with hepatic and renal failure may be agitated, they are usually not appropriately responsive (12). Furthermore, control of agitation in these patients must be dealt with carefully because of altered metabolism and elimination of pharmaceutical agents.

Last to be mentioned in the enumeration of differential diagnosis of agitation is nonclinical seizure activity, which may lead to significant degrees of agitation and may be difficult to differentiate from typical seizures. Usually, an EEG will be necessary to make the diagnosis. In patients who have suffered an anoxic injury, a clonic seizure-like activity must also be differentiated from that which is secondary to hypoxic injury to the brain, and not actually a seizure.

MONITORING AGITATION AND BEDSIDE DECISION MAKING

Anxiety and agitation are common in the ICU. Despite the frequency of their occurrence in the acutely ill patient, a clear definition, assessment strategy, or treatment plan often remain unclear to the bedside practitioner. Agitation is subject to interpretation by the individual clinician, thereby making it difficult to objectify and monitor from caregiver to caregiver. Despite the proliferation of literature in recent years, confusion still exists among physicians, nurses, and other ICU staff with regard to a common definition of agitation, its incidence and causes, the role of environmental factors, the relationship to ICU LOS, and the role of drugs and interventions being employed in the ICU. Establishing a multidisciplinary standard of care for assessing, treating, and monitoring agitation in the ICU is imperative for optimal patient management and improved outcomes.

Anxiety/Agitation Continuum

In the critically ill patient, agitation can be described along a continuum of continuously changing physiologic states with varying behaviors and responses, affecting each patient differently within the severity and complexity of their condition. For most ICU practitioners, a very brief description or assessment by an experienced staff member at the bedside can provide a wealth of information for reaching decisions with respect to the status of the patient, variables causing agitation, and intervention. The signs and symptoms of agitation are fairly obvious. Descriptive terms commonly used include restlessness; thrashing around in bed; pulling at catheters, tubes, and restraints; overbreathing the ventilator; and asynchrony with the current ventilator settings. Abnormalities in vital signs include tachycardia, tachypnea, and hypertension.

Scales and Tools to Monitor Agitation

Patients in the ICU typically demonstrate complex disease states with a rapidly changing hemodynamic status, making their requirements for treatment of agitation fluctuate over time. These constantly changing requirements foster the need for bedside clinicians to reassess and redefine the goals of therapy frequently. The ideal scale or tool to monitor agitation in the ICU should therefore be simple to apply, yet describe clear graded changes between levels to allow titration of interventions depending on the condition of the patient.

Numerous scales and tools to monitor the degree of agitation in clinical practice are described in the literature. Most of these instruments attempt to evaluate a single item, such as level of consciousness, at a single point in time. Others combine level of consciousness with descriptive responses to interventions, such as mechanical ventilation. Unfortunately, there is no gold-standard method to evaluate ICU patient response to agitation therapy (13). Despite the weaknesses of some of the monitoring tools, applying them to protocol-driven intervention plans has been shown to improve patient outcomes, such as duration of mechanical ventilation and ICU LOS (14).

The most commonly used scale in current literature is the Ramsay Sedation Scale (15). The Ramsay scale identifies six levels of sedation ranging from *frank agitation* to *deep coma* (see Table 2). Despite its frequent use in research, the Ramsay scale exhibits shortcomings when applied at the bedside of patients with complex problems. The six levels of sedation in the Ramsay scale are not mutually exclusive of one another; for example, the patient may appear to be asleep with a sluggish response to glabellar tap (Ramsay 5) yet restless and anxious (Ramsay 1).

The Riker Sedation-Agitation Scale (SAS) was the first scale formally tested for reliability and validity in the ICU (see Table 3). The SAS identifies seven symmetrical levels, ranging from dangerous agitation to deep sedation. This scale provides descriptions of patient behavior in varying levels that assist the bedside practitioner in distinguishing between the levels (2).

The Motor Activity Assessment Scale (MAAS), which is similar in structure to the SAS, uses patient behaviors to describe the different levels of agitation (16). The MAAS identifies seven levels ranging from unresponsive to dangerously agitated (see Table 4).

The Confusion Assessment Method for ICU (CAM-ICU) described recently by Ely and colleagues (17) is being validated in critically ill patients with delirium (see Table 5). This tool for delirium has been tested in combination with a sedation scale or the Glasgow Coma Scale (GCS) for challenging patients and found to be simple to apply at the bedside, with inter-rater reliability, sensitivity, and specificity. The effect on therapeutic intervention using this scale is still being evaluated.

The development of noninvasive, objective monitors of brain function using EEG signals may lead to a more standardized assessment of agitation and sedation. This objective monitor is especially helpful in the deeply sedated patient receiving neuromuscular blockade, as subjective scales requiring patient input are not valid. The Bispectral Index (BIS) provides a discrete value from 100 (completely awake state) to <60 (deep sedation) and ≤ 40 (deep hypnotic state or barbiturate coma) by incorporating several EEG components (18). Although the technique has been shown to be a valid and reliable measure in the operating room (19), it has not been studied to any great extent in the ICU. In one study designed to determine whether BIS correlates with responses to commands during sedation and hypnosis induced by propofol, and to compare BIS with targeted and measured concentrations of propofol in predicting participants' responses to commands, 20 volunteers were given propofol infusions and EEGs were recorded for off-line analysis of BIS. The results showed that the BIS is an accurate predictor of response to verbal commands during sedation and hypnosis with propofol. Accuracy was maintained when propofol concentrations were increased or decreased and when repeated measurements were made over time (20). Additional studies are needed for BIS or other objective monitoring tools before acceptance into clinical practice (18).

Table 2. Ramsay scale for assessing level of sedation

Level	Response
1	Patient awake and anxious, agitated, and/or restless
2	Patient awake, cooperative, accepting ventilation, oriented, and tranquil
3	Patient awake, responds to commands only
4	Patient asleep; brisk response to light glabellar tap or loud auditory stimulus
5	Patient asleep; sluggish response to light glabellar tap or loud auditory stimulus but does respond to painful stimulus
6	Patient asleep, no response to light glabellar tap or loud auditory stimulus

Table 3. Sedation-Agitation scale (2)

Score	Diagnosis	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits, requires physical restraints, bites endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Table 4. Motor Activity-Assessment scale (16)

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimulus
1	Responsive only to noxious stimuli	Opens eyes *or* raises eyebrows *or* turns head toward stimulus *or* moves limbs with noxious stimulus
2	Responsive to touch or name	Opens eyes *or* raises eyebrows *or* turns head toward stimulus *or* moves limbs when touched or name is loudly spoken
3	Calm and cooperative	No external stimulus is required to elicit movement, *and* the patient is adjusting sheets or clothes purposefully and follows commands
4	Restless and cooperative	No external stimulus is required to elicit movement, *and* the patient is picking at sheets or clothes *or* uncovering self and follows commands
5	Agitated	No external stimulus is required to elicit movement *and* attempting to sit up *or* moves limbs out of bed *and* does not consistently follow commands
6	Dangerously agitated, uncooperative	No external stimulus is required to elicit movement, *and* patient is pulling at tubes or catheters *or* thrashing side to side *or* striking at staff *or* trying to climb out of bed *and* does not calm down when asked

Bedside Decision-Making

Various factors and processes may influence assessment and treatment practices in the ICU. There is little in published literature concerning this topic. Weinart et al. (21) conducted focus group interviews with ICU nurses at two hospitals and described factors affecting nurses' delivery of sedative therapy. Key factors identified as impacting sedative therapy included nursing attitudes and beliefs about critical illness, family members' perception of agitation, and nurses' workload and staffing ratios.

Table 5. Confusion assessment method for the intensive care unit (17)

Feature 1. Acute onset of mental status changes or fluctuating course
- Is there evidence of an acute change in mental status from the baseline?
- Did the (abnormal) behavior fluctuate during the past 24 hrs, that is, tend to come and go or increase and decrease in severity?
- Did the sedation scale (e.g., Sedation-Agitation scale or Motor Activity-Assessment scale) or coma scale (Glasgow Coma scale) fluctuate in the past 24 hrs?

Feature 2. Inattention
- Did the patient have difficulty focusing attention?
- Is there a reduced ability to maintain and shift attention?
- How does the patient score on the Attention Screening Examination, or ASE (i.e., visual component ASE tests the patient's ability to pay attention via recall of ten pictures; auditory component tests attention via having patient squeeze hands or nod whenever the letter "A" is called in a random letter sequence)?

Feature 3. Disorganized thinking
- If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.
- For those still on the ventilator, can the patient answer the following four questions correctly?
  - Will a stone float on water?
  - Are there fish in the sea?
  - Does 1 pound weigh more than 2 pounds?
  - Can you use a hammer to pound a nail?
- Was the patient able to follow questions and commands throughout the assessment?
  - "Are you having any unclear thinking?"
  - "Hold up this many fingers" (examiner holds two fingers in front of patient).
  - "Now do the same thing with the other hand" (not repeating the number of fingers).

Feature 4. Altered level of consciousness

Any level of consciousness other than alert (e.g., vigilant, lethargic, stupor, or coma).

Alert:	Normal, spontaneously fully aware of environment, interacts appropriately
Vigilant:	Hyperalert
Lethargic:	Drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
Stupor:	Difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into the unresponsive state
Coma:	Unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is impossible even with maximal prodding

Patients are diagnosed with delirium if they have Features 1 and 2 as well as *either* Features 3 or 4.

Teaching bedside staff the critical decision-making skills necessary to optimally manage agitation is an important responsibility of all critical care educators. With respect to assessing the agitated patient, there are some simple considerations that need to be made quickly and effortlessly by every bedside caregiver. One of the first things to be considered is whether there is an underlying physiologic cause for the observed agitation symptoms. For example, disease-related pain and hypoxemia are two common causes of agitation in the ICU. Interventions focused to correct the medical condition will therefore resolve the agitation. Another factor to be considered on initial assessment is the possibility of any ongoing therapy being the cause of the agitation. For example, the patient may be exhibiting a medication-related side effect, a malfunctioning nasogastric tube causing feelings of nausea and agitation, or a blocked Foley catheter. Other initial considerations must include the possibility that agitation may be a result of withdrawal symptoms from either medications administered before ICU admission or abuse of alcohol or illicit drugs. After exclusion of obvious causes of agitation, considerations with regard to the hemodynamic stability of the patient will affect speed of bedside staff intervention, and the determination of requirements for immediate pharmacologic therapy or, alternatively, whether nonpharmacologic strategies may be appropriate to treat agitation (8, 11, 22).

Once the bedside staff has ruled out obvious causes and identified the severity of the agitation, considerations regarding optimal interventions can be made to ensure the best patient outcomes. Pharmacologic agents such as benzodiazepines or propofol are frequently administered in the ICU to treat agitation; however, most bedside caregivers also employ nonpharmacologic interventions. These interventions include optimizing communication with the patient, coaching the patient in relaxation techniques, reorienting the patient to the unit, reducing environmental stimuli and noise, and providing psychosocial support (6). Critically ill patients exhibit severe sleep fragmentation and reduced restorative sleep with suppression of rapid eye movement. The exact etiology and pathophysiology of sleep disruption in the ICU remains unknown. Regardless of the cause, serious adverse effects are associated with sleep deprivation, including impaired immunity, impaired protein synthesis, respiratory abnormalities, and disrupted thermoregulation. Patients in the ICU often consider sleep disruption to be one of the most unpleasant aspects of their illness (23).

Patient-specific goals for therapy can be defined to ensure desired endpoints. These goals are often linked to the indications for therapy—for example, treatment of anxiety or agitation, abolishing discordance with the ventilator, reducing oxygen consumption, or as an adjunct to neuromuscular blocking agents.

Establishing and Implementing Sedation Guidelines and Protocols

The successful development and implementation of sedation guidelines and

protocols require multidisciplinary input and additional training for all caregivers; physicians and nurses need to agree on monitoring scales and tools and then insure that these scales are used reliably across disciplines and within units. It is essential to determine specific details regarding the frequency of assessment, predefined end points of therapy, and evaluation of patient outcomes. Forms and flow sheets currently in use at the bedside can be used for developing documentation systems. Using these documentation systems to foster communication between disciplines (e.g., nurse to physician) and within disciplines (shift to shift) assures uniformity of guidelines. Development of drug administration guidelines that foster current pharmacologic/pharmacokinetic recommendations and standards for acutely ill patients is encouraged.

Brook et al. (14) conducted a randomized, controlled trial of patients in a medical ICU that compared protocol-directed with nonprotocol-directed sedation administration. Patients in the protocol-directed group had less time on mechanical ventilation, shorter ICU LOS, and shorter hospital LOS, as well as decreased need for tracheostomy compared with those in the nonprotocol-directed group. These results demonstrate that using a multidisciplinary-designed sedation protocol can improve patient outcomes and decrease overall cost. Other bedside strategies to optimize outcomes in patients receiving therapy for agitation in the ICU include instituting daily reassessment and interruptions of sedative infusions (23). Daily interruption of sedative infusions was found to decrease duration of mechanical ventilation (4.9 days compared with 7.3 days), decrease ICU LOS, and improve clinicians' ability to perform daily neurologic examinations, therefore reducing the need for diagnostic studies to evaluate unexplained alterations in mental status.

Regulatory Issues

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) reinforces the importance of appropriate sedation in its revised Standards and Intents for Sedation and Anesthesia Care, effective January 1, 2001 (24). Institutional compliance with these revised standards requires the institution to ensure that all individuals administering sedation be qualified and have appropriate credentials to manage patients receiving moderate or deep sedation. In these revised standards, the levels of sedation have been defined by JCAHO as follows:

- Minimal sedation is a drug-induced state during which patients respond normally to verbal commands, although cognitive function and coordination may be impaired; ventilatory and cardiovascular functions are unaffected.
- Moderate sedation is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
- Deep sedation is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Verification of compliance with the standard requires the institution to provide monitoring standards and assessment tools within its policies for care. Institution-wide agreement regarding the standard of care for sedation practice requires ensuring the competency of all staff caring for patients requiring sedation. Evidence of multidisciplinary teaching strategies including sedation assessment parameters, documentation tools, and evaluation of patient outcomes is suggested throughout all areas of the institution in which sedation is administered (*CAMH* update, 3 August 2000: *Comprehensive Accreditation Manual for Hospitals*, effective 1/1/01). Application of the current critical care literature, including the use of protocols, algorithms, assessment tools, and delivery strategies, reinforces these regulatory standards.

ICU SEDATIVE PHARMACOLOGY UPDATE: A REVIEW OF COMMONLY USED AND EMERGING AGENTS

Analgesics and sedatives are mainstays of supportive patient care in the ICU. Critically ill patients are frequently in pain as a result of their medical condition or surgery; mechanical ventilation and environmental factors cause additional stresses. Delirium and other adverse effects of the ICU stay necessitate the use of sedation to prevent or alleviate the agitation that commonly results. Analgesia is important for the same reason: severe pain is a frequent cause of agitation and delirium.

It is generally recommended that patients in the ICU receive sufficient analgesia, usually with opiates, before sedatives are administered. Traditionally, benzodiazepines such as midazolam, lorazepam, and diazepam have been used for sedation, whereas haloperidol has been used to treat delirium. More recently, propofol has become a popular drug for ICU sedation; the introduction of emerging sedative agents, such as dexmedetomidine and potentially 2% propofol, will further broaden clinician options.

The choice of an appropriate sedative is often difficult, and depends on the individual needs of the patient. For example, if rapid awakening to a state of alertness is required, as in the neurologic patient who requires frequent monitoring, propofol is the preferred agent. For long-term sedation, lorazepam is considered the drug of choice. Haloperidol is the preferred agent for delirium. It is essential that practitioners become familiar with the properties and uses of these agents so that the patient is given the opportunity for the best outcome.

Maintenance of adequate sedation is a key component of ICU care. Ventilatory support frequently induces anxiety, pain, and asynchrony. Appropriate sedatives and analgesics can alleviate much of this discomfort, and can lessen stress-induced increases in oxygen consumption. In patients with respiratory failure, the administration of sedatives at appropriate doses helps increase chest wall compliance, allows the manipulation of inspiratory to expiratory ratio and other variables, improves oxygenation, and reduces desynchronized breathing (25, 26).

Alleviation of pain is an equally important component of care in the ICU. An increased level of pain activates the sym-

pathetic nervous system, placing additional demands on the cardiovascular system in critically ill patients. When pain is prolonged, it contributes to severe anxiety and even delirium. The hypermetabolic state after injury is exacerbated by pain, potentially leading to diminished immune function and impaired wound healing. Therefore, adequate analgesia is of essential importance in the management of these patients (27).

The primary goals of sedative therapy, once a pain-free state is achieved, are anxiolysis, hypnosis, and amnesia. Not all sedative agents used in the ICU can achieve these goals, making the correct choice of a sedative of paramount importance. Similar plasma concentrations of a given sedative can have varied results in different individuals with respect to drug disposition and pharmacodynamic effect. The doses of drug required for adequate sedation also change during the ICU stay based on the nature and course of the disease, interaction of the sedative with other pharmacologic agents, and the response to therapy. No single depth of sedation or single sedative agent is appropriate for all patients (27).

Sedatives are not used only for sedation in the ICU; other indications include management of drug withdrawal syndromes and treatment of seizures. Proper use of these agents can enhance patient comfort and safety, but, if inappropriately chosen or incorrectly administered, the occurrence of side effects can lead to increased morbidity, mortality, and costs (28) (Table 6).

The practice parameters for intravenous (iv) sedation in the ICU published in 1995 by the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) have been updated to include an evaluation of the literature published since 1994 comparing the use of sedatives and analgesics in the ICU. Now known as Clinical Practice Guidelines, the 2001 guidelines recommend that sedation of critically ill patients be started only after provision of adequate analgesia and treatment of reversible physiologic causes. For rapid sedation of acutely agitated patients, midazolam or diazepam should be used. Propofol is the preferred sedative when rapid awakening (as for neurologic assessment or extubation) is important (29). Midazolam is recommended for short-term use only, as it produces unpredictable awakening and/or time to extubation when infusions continue for more than 48–72 hrs. For intermittent iv doses or continuous infusion, the recommended drug for sedation in most patients is lorazepam (30, 31). Haloperidol is the preferred agent for the treatment of delirium in critically ill patients (32).

Guidelines have been implemented to standardize care and lower costs, and an increasing number of hospitals have adopted them for use in ICU sedation. Mascia et al. (33) and Devlin et al. (34) examined the impact of guidelines on costs and outcomes.

Mascia et al. (33) performed a prospective cost-effectiveness analysis. Tracking of 72 eligible baseline (preguidelines) patients was followed by the development and introduction of guidelines developed with multidisciplinary input, along with an academic detail process to promote their use. Several months following the introduction of these guidelines, a second group of 84 follow-up (postguidelines) patients was tracked. Both groups were similar with regard to number of regimens and days of treatment. Ventilator time and LOS were shorter in the postguidelines group, without a compromise in quality of care, and drug costs were significantly reduced in the postguidelines group. The costs of propofol when given for 24 hrs or longer, for example, were $355.82 to $1,010.85 for the preguidelines group and $123.06 to $460.50 for the postguidelines group. Total sedation costs were reduced from $4,515 to $1,152 ($p = .081$) (33).

The Devlin study (34) was designed as a before-and-after study in a 15-bed medical-surgical ICU. Guidelines were developed through a consensus of physicians, nurses, and pharmacists. Fifty patients were evaluated before the guidelines were developed, and 50 were evaluated after the guidelines were implemented. The guidelines promoted the use of lorazepam over midazolam, with propofol suggested for patients not successfully sedated with high-dose lorazepam, haloperidol, or morphine. Over the 2-month study period, there was no difference in the median weaning time for the two groups. Total sedation costs, however, decreased from $4,515 in the preguidelines group to $1,152 in the postguidelines group ($p = .081$). The median per-patient sedation drug cost decreased from $11.27 (range, $0–1,340) in the preguidelines group to $3.55 (range, $0–250) in the postguidelines group. The number of postguidelines patients receiving continuous infusions was significantly less than preguidelines patients (14% vs. 56%, respectively; $p < .05$). Although it did not reach significance, there was a trend for fewer postguidelines patients to receive neuromuscular blocking agents in the ICU (4% vs. 8%). This study demonstrated that high compliance with ICU sedation guidelines led to a 75% decrease in sedation drug costs (34).

Table 6. Properties of an ideal sedative (29–31)

Easily titratable level of adequate sedation
Rapid onset of action
Short acting, allowing patient assessment, easy weaning from mechanical ventilation, and early extubation
No adverse effects
No nausea, vomiting, phlebitis
No anaphylaxis or allergic reaction
Minimal metabolism; not dependent on normal hepatic, renal, or pulmonary function
No active or toxic metabolites
No suppression of cortisol production by the adrenal cortex
No interactions or incompatibilities with other commonly prescribed intensive care unit drugs
Ease of administration
Lack of accumulation with prolonged administration
Does not promote growth of pathogens
Cost effective
Easily prepared and long shelf-life

Opioids

Opioids are the primary agents used for analgesia in the ICU. They are lipid-soluble and bind to opiate receptors in the central and peripheral nervous system. At low doses, opioids provide analgesia but not anxiolysis, whereas at higher doses they act as sedatives. All opioids share therapeutic properties but vary in potency and pharmacokinetics. Morphine, but not fentanyl, induces histamine release, which results in hypotension. Although opioids can be given by several routes, the iv method is preferred in the ICU for reliable drug delivery. When given

in iv therapeutic doses, opioids cause sedation, in the sense of a clouded sensorium. They do not, however, possess amnestic properties (9, 35, 36).

Opioids are stereospecific agonists at endorphin receptor sites in the central nervous system and other tissues. Mu-1 receptors are believed to mediate the supraspinal analgesic action of opioids, whereas agonism at mu-2 receptor sites is thought to produce side effects including ventilatory depression, bradycardia, and physical addiction. All drugs in this class primarily undergo hepatic metabolism. Aside from analgesia, an important neurophysiologic effect of opioids is respiratory depression. The respiratory rate, minute ventilation, and the sensitivity of the medullary respiratory center to CO_2 all decrease after administration of opioids (37).

Morphine sulfate is the prototypic opioid and is the preferred opioid analgesic in patients with stable hemodynamics. It has lower lipid solubility than does fentanyl; the result is a delayed onset of action. Morphine induces the release of histamine, which increases the likelihood of hypotension secondary to vasodilatation (9, 39). A metabolite of morphine, morphine-6-glucuronide, is excreted in the urine and may accumulate in renal failure. The opiate activity of this metabolite is several times greater than that of morphine, and its accumulation in patients with renal failure has been reported to prolong narcosis (37).

Fentanyl citrate, a synthetic narcotic analgesic up to 100 times more potent than morphine, is highly lipid-soluble and has a rapid onset of action because it quickly crosses the blood-brain barrier. This drug has no active metabolites and is not associated with histamine release or venodilating effects. Because of these characteristics, fentanyl is the recommended opioid as second-line therapy in patients with unstable hemodynamics or those who cannot tolerate the adverse effects of morphine. Fentanyl should be administered by continuous infusion for sustained effect because of its short duration of action (35, 38).

Hydromorphone is a highly potent opioid with no active metabolites. Hydromorphone can be used during shortages of fentanyl because it has no active metabolites and does not cause clinically significant histamine release. Remifentanil, an extremely short-acting opioid analgesic with a rapid onset of action, is rarely used in the ICU setting. Meperidine should be avoided in the ICU because of the neuroexcitatory properties of its metabolite that accumulates in renal failure (35, 39).

The use of opioids is associated with undesirable side effects. Because all opioids produce respiratory depression, weaning may be difficult in patients receiving these agents. The incidence of hypotension varies with the opioid and its properties with respect to vasodilatation and histamine release. Gastrointestinal side effects include slowing of gastrointestinal motility; this can lead to ileus, gastric distention, nausea, and vomiting. Naloxone, an opioid antagonist, is much shorter-acting than most opioids and is the most widely used narcotic antagonist in the ICU for reversal of side effects. Dependence and withdrawal can be a problem in patients receiving long-term opioid therapy in the ICU. Sudden discontinuation of therapy to prepare a patient for extubation may result in the development of withdrawal symptoms. Tapering the dose, while monitoring for signs of withdrawal, is recommended in all ICU patients who have been on long-term opioid therapy (9, 35).

Benzodiazepines

The class of agents most widely used for sedation in the ICU is the benzodiazepines (see Table 7) (40). These drugs provide anxiolysis and amnesia, but they have no analgesic properties. The two predominant mechanisms of action of benzodiazepines within the nervous system involve activity at γ-aminobutyric acid (GABA) receptors. Potentiation of GABA-mediated transmission by benzodiazepines is apparently responsible for the somnolent, anxiolytic, and anticonvulsant actions, whereas the amnestic property seems to correlate with GABA agonist activity in the limbic cortex (38). The benzodiazepines currently used in the ICU setting are diazepam, lorazepam, and midazolam. The primary difference between these agents relates to their pharmacokinetics.

The liver extensively clears benzodiazepines. The effects of these drugs may be prolonged in critically ill patients because of decreased metabolism or in the presence of severe liver disease. Because benzodiazepines are sequestered in fat stores, prolonged sedation may occur with chronic administration (37). The effects of benzodiazepines can be reversed by flumazenil, a competitive antagonist with a rapid onset and relatively short duration of action in comparison with the prolonged effects of benzodiazepines (38).

Withdrawal syndromes are known to occur after continued use of benzodiazepines, and tachyphylaxis can develop within hours to days. The latter requires either dose escalation or use of another sedative agent. After several weeks of continued use, the acute cessation of therapy can give rise to a syndrome that manifests as tremors, diaphoresis, photophobia, insomnia, abdominal discomfort, hypertension, and seizures (37).

Diazepam is a long-acting lipophilic benzodiazepine that rapidly penetrates the central nervous system, so that sedative effects are seen within 2–3 mins. Although diazepam is no longer recommended for routine use in the ICU, there are reports of its use for long-term sedation in selected patients (32). This recommendation is the result of a scheduled intermittent dosing regimen that may easily lead to excessive and prolonged sedation. Also, dilution is needed for continuous infusion, and this usually requires large volumes of fluid administration. Other disadvantages of diazepam are the common occurrence of pain and thrombophlebitis when the drug is administered by peripheral vein injection (39). Diazepam has an active metabolite, dimethyl-diazepam, which is only slightly less potent than diazepam and has an elimination half-life of 96 hrs, longer than that of the parent compound (37).

Table 7. Pharmacokinetics of diazepam, lorazepam, midazolam, and propofol in healthy volunteers

	Diazepam	Lorazepam	Midazolam	Propofol
Half-life (α), min	30–66	3–20	6–15	2–3
Half-life (β), hrs	24–57	14	1.7–2.6[a]	0.5–1.0
Volume of distribution, L/kg	0.7–1.7	1.14–1.3	1.1–1.7	5.4–7.8
Clearance, mL/kg/min	0.24–0.53	1.05–1.1	6.4–11.1	26–29
Protein binding, %	96–99	86–93	97	98
Active metabolites	Yes	No	Yes	No

[a]Up to 30 hrs in patients in the intensive care unit. Adapted from Young, 2000, Table 3.

Lorazepam, an intermediate-acting benzodiazepine, is less lipophilic than diazepam and therefore has less potential for accumulation. The drug is usually administered by intermittent iv injection, but continuous infusion may be used. Because there is a slight delay in the onset of action of lorazepam, it is acceptable to administer a single dose of a more rapidly acting benzodiazepine when achievement of rapid sedation is necessary. Compared with midazolam, lorazepam is longer acting, causes less hypotension, produces equally effective anterograde amnesia, and, with prolonged administration, produces more rapid awakening (39). The new *Clinical Practice Guidelines* recommend lorazepam for the sedation of most patients by intermittent iv doses or continuous infusion (32). The drug has no active metabolites and its metabolism is less affected by advanced age or liver dysfunction compared with midazolam. Lorazepam is associated with a stable hemodynamic profile, even when opioids are concurrently administered (41). It may, however, be unstable in solution and can precipitate in iv catheters and tubing, particularly if infusions last longer than 12 hrs. This can add to the cost of therapy. Propylene glycol toxicity, marked by acidosis and renal failure, has occurred with higher doses of lorazepam or prolonged infusion of the drug (27). There was recently a case report in *Pharmacotherapy* of propylene glycol toxicity of lorazepam in only 3 days in a patient with renal failure (first case in <72 hrs of therapy (42).

Midazolam is a short-acting, water-soluble benzodiazepine that is transformed to a lipophilic compound in the blood. The drug rapidly penetrates the central nervous system to produce a short onset of sedation of 2–5 mins. Its duration of effect is brief because it is rapidly redistributed, a property that favors continuous infusion for maintenance of sedation (39). Use of midazolam for chronic sedation is limited because, in some patients, there is prolonged elimination half-life of up to 30 hrs and associated variability in the time of return to consciousness after discontinuation; however, few adverse hemodynamic and respiratory effects are seen with the short-term use of midazolam. To minimize the incidence of withdrawal phenomena after long-term duration infusions, the drug should be properly tapered (41). The new *Clinical Practice Guidelines* recommend midazolam for rapid sedation of acutely agitated patients. It is recommended for short-term use only, as it produces unpredictable awakening and/or time to extubation when infusions continue for more than 48–72 hrs (32).

Midazolam exhibits dose-related hypnotic, anxiolytic, amnestic, and anticonvulsant actions. The drug also causes dose-related respiratory depression, and at large doses can cause hypotension and vasodilatation. When midazolam is administered as a continuous infusion, however, these effects are minimal (27). The drug is biotransformed to an active metabolite in the liver that is not as potent and is shorter-lasting than the parent compound. Because only small quantities are formed during continuous infusion of midazolam, this metabolite does not contribute significantly to the pharmacologic activity of the drug (except in patients with severe renal failure) (27). The metabolism of midazolam is reduced when administered to patients receiving cytochrome P-450 3A4 inhibitors such as erythromycin and fluconazole (43).

Midazolam infusions for sedation have been compared with other benzodiazepines. In a prospective randomized study, Pohlman et al. (44) compared the efficacy of continuous infusions of midazolam (mean dose, 0.24 mg/kg/hr) and lorazepam (mean dose, 0.06 mg/kg/hr) for sedation of mechanically ventilated patients in a medical ICU. For both drugs, the time to achieve sedation was often prolonged, and higher doses than those reported in the literature were required to maintain sedation. Time to awakening was occasionally delayed for more than 24 hrs after discontinuation of either infusion, and large volumes of fluid were needed to deliver the required doses. In addition, patients treated with midazolam had a tendency to return more slowly to baseline mental status. There was equally effective sedation and no difference in other clinical variables. The relative potency of lorazepam was two to four times greater than that of midazolam. Despite a standard protocol for sedation in this study, the mean time to achieve adequate sedation was 115 mins for the entire study group, which the investigators suggest was the result of patient dose-effect variability, poorly developed dosing guidelines, and the changing clinical condition of ICU patients.

Propofol

Propofol is a sedative-hypnotic with no analgesic action (37); it has sedative, hypnotic, and anxiolytic properties (39). Other effects of propofol are bronchodilation, seizure suppression, muscle relaxation, and possible anti-inflammatory and antiplatelet effects. Propofol is highly fat soluble, and hence is formulated in an intralipid, a 1% emulsion containing 10% soya bean oil, 2.25% glycerol, and 1.2% purified egg phosphatide (37). A 2% formulation of propofol is currently under Food and Drug Administration (FDA) evaluation.

After a single iv dose, the onset of action of propofol is rapid (1–2 mins) and its effect is brief (10–15 mins) because of rapid central nervous system penetration and subsequent redistribution. Therefore, propofol is administered only by continuous infusion when used for sedation. Long-term infusion results in accumulation within lipid stores, so that there is a prolonged elimination phase with a half-life of up to 300–700 mins. However, subtherapeutic plasma concentrations of the drug are maintained after discontinuation because of rapid clearance, thus limiting the clinical significance of this half-life value (39). Although the mechanism of action of propofol is still not completely understood, the drug appears to activate the GABA-A receptor within the central nervous system. Propofol alters the sensorium in a dose-dependent manner, from light sedation to general anesthesia. The drug is also a potent respiratory depressant, causing a reduction in systemic vascular resistance and possibly hypotension, especially when administered as a bolus. Parallel with its action on the level of arousal, propofol decreases cerebral metabolism, which results in a coupled decline in cerebral blood flow and a decrease in intracranial pressure. Sedative infusion doses of this agent typically result in minimal hemodynamic alteration with no change in perfusion pressure as long as adequate intravascular volume status is maintained (37).

Propofol is considered an ultra short-acting agent for two reasons. Because it is highly lipophilic, the drug redistributes to fatty tissues to such an extent that its volume of distribution approaches 600–800 L. Second, drug clearance is calculated to be more than 1.5–2.0 L/min, exceeding hepatic blood flow and suggesting possible extrahepatic metabo-

lism. These kinetics result in a very rapid uptake and elimination from plasma with little accumulation and a low likelihood of delayed recovery from sedation. Despite maintenance of propofol sedation for up to several days, recovery to an awake and responsive state after discontinuation of therapy occurs within 10–15 mins (37). The pharmacokinetics of propofol are not altered in patients with renal or hepatic disease (36).

The use of propofol is not currently recommended for pediatric patients in the ICU because of reports of metabolic acidosis with accompanying lipemic serum, bradyarrhythmias, and fatal myocardial failure; this occurred in patients being treated with excessively high doses (45). In adults, prolonged high-dose infusion may also lead to cardiac failure (31, 46).

Several studies have compared midazolam with propofol infusions for sedation in medical, surgical, and coronary ICUs (47–58). Both drugs are generally safe and effective in the early postoperative period. Patients sedated with propofol infusions recover more rapidly, with less variability in recovery times, compared with patients sedated with midazolam infusions. Furthermore, alterations in the level of sedation are controlled more easily with propofol than with midazolam infusions. There is no difference in the quality of sedation. In patients treated with propofol, especially with a loading dose, there has been observed an increased incidence of hypotension compared with midazolam, and therefore a bolus is not recommended (41). In most of these studies, the time from drug discontinuation to successful ventilator weaning was significantly shorter for patients receiving propofol.

Barrientos-Vega et al. (59) conducted an open-label, randomized, prospective, phase IV clinical trial to evaluate the impact of prolonged sedation of critically ill patients with midazolam or propofol on weaning and ICU costs, using a cost-of-care approach. This trial, conducted in the medical and surgical ICU of a community hospital in Spain, included 108 patients requiring mechanical ventilation for at least 24 hrs. Although both drugs provided equivalent sedation, administration of propofol was associated with a shorter weaning time than midazolam, resulting in a more favorable economic profile. The midazolam group showed a higher rate of patients exhibiting inadequate sedation, whereas the propofol group showed a higher rate of therapeutic failure when cases of hypertriglyceridemia were factored in. Neither difference reached statistical significance. Propofol infusion was also associated with an earlier extubation time than midazolam, including not only the time to awakening, but also time from the first T-bridge trial to extubation.

The same investigators conducted another study comparing propofol 2% and propofol 1% with respect to effectiveness and wake-up time required for prolonged sedation. Results were then compared with the results of the earlier study comparing propofol 1% and midazolam. Sedation with either propofol formulation was associated with a more rapid weaning time and more predictable wake-up than sedation with midazolam, although the differences did not reach statistical significance. The cost-effectiveness profile of both propofol concentrations was better than that of midazolam. Differences were significant for up to 288 hrs of sedation for the propofol 1% group and up to 312 hrs of sedation for the propofol 2% group. The economic benefits of propofol vs. midazolam were associated with shorter weaning time and shorter ICU stays, whereas the economic benefits of propofol 2% were associated with reduced frequency of hypertriglyceridemia compared with propofol 1% (60).

Carrasco et al. (61), in another trial conducted in Spain, compared the efficacy, safety, and cost of propofol and midazolam for short-, medium-, and long-term sedation of critically ill patients. The study randomized 88 patients to short-term (<24 hrs), medium-term (24 hrs to 7 days), and prolonged (>7 days) continuous sedation with propofol (n = 46) or midazolam (n = 42). In the short-term sedation subgroups, time to extubation and time elapsed until normalization of the alertness level were significantly shorter in patients treated with propofol ($p < .05$). In the medium-term sedation subgroups, the average sedation time was similar in both groups. Recovery time until extubation and time elapsed until reaching normal alertness levels were significantly shorter in patients infused with propofol ($p < .05$). In the long-term sedation subgroups, the mean sedation time was similar in both subgroups, but recovery time until extubation and time elapsed to reach normal levels of alertness were significantly shorter in patients in the propofol group. Although the cost of propofol was higher than that of midazolam in all three treatment groups, the longer ICU stay required with midazolam resulted in postsedation care costs higher than the costs for the propofol group. These findings indicate that propofol is a sedative agent with equivalent safety yet higher clinical effectiveness and better cost-effectiveness ratio than midazolam in the continuous sedation of critically ill patients (61).

Although these studies indicate that the costs of sedation with propofol are lower than those with midazolam in the ICU, more studies of this type are needed to further assess the true cost of these agents.

A more consistent recovery rate was seen with propofol than with midazolam. For infusions of <4 days, propofol recovery time was often related to the duration of sedation, whereas midazolam recovery time was not. After discontinuation of the drug, most of the patients receiving propofol recovered in 1 hr or less, whereas most of the patients receiving midazolam took from several hours to 10 days for similar recovery after deep sedation. Propofol has not been compared with lorazepam in a clinical trial. Such a study, however, may be difficult to implement inasmuch as propofol is used for short-term sedation whereas lorazepam is used in the long term. Side effects associated with propofol sedation include hypotension, which is more common with rapid dose escalation or iv bolus doses, bradycardia, and hypertriglyceridemia, which appears to occur with higher infusion rates (35).

A new formulation, 2% propofol, which is twice as concentrated as the available 1% formulation, is currently undergoing end-stage FDA review for use as a sedative in the ICU. The rationale for this new formulation is that, by doubling the concentration, the fat load will be reduced by half while maintaining the same sedative efficacy, thus lessening the likelihood of increased serum levels of triglycerides. Ewart et al. (63) conducted a feasibility study comparing 2% propofol with the 1% formulation in 40 patients (20 in each treatment group) undergoing mechanical ventilation in an ICU after coronary artery bypass surgery. No significant differences in the amount of propofol used, the rate of infusion, and the numbers of changes in infusion rate, recovery time, and time to extubation was found between the two formulations. However, mean heart rates of patients

receiving 2% propofol were significantly higher throughout the study.

A study conducted by McLeod et al. (64) was designed to determine serum concentrations of lipids during infusion of 2% propofol for 50 hrs in 30 ventilated surgical, trauma, and medical patients in an ICU. The triglyceride concentration did not significantly increase over a 50-hr period, and both mean cholesterol and high-density lipoprotein levels were low. There was a direct correlation between triglyceride and C-reactive protein concentration, and an inverse correlation between cholesterol and C-reactive protein, which suggests that lipid changes in critically ill patients may be in part related to the acute-phase response. The investigators suggest that, to avoid fat overload in critically ill patients, administration of additional lipids be adjusted to account for the lipid content of propofol. Some studies show higher propofol requirements in first few days of sedation therapy with use of 2% propofol. The reason for this remains to be determined.

Within 1 yr of the introduction of propofol in the United States in 1989, reports appeared of clusters of infections in surgical patients who had received propofol (65). This resulted in the inclusion of an additive to help retard growth of microorganisms. The additive, ethylenediaminetetraacetic acid (EDTA), at a concentration of 0.005%, has no effect on the physical or chemical stability of the emulsion components. In the 4 yrs since the introduction of this modified propofol preparation, clinical experience in more than 30 million patients in the United States has demonstrated a reduction in the incidence of fevers and infections from approximately 20 per year to essentially zero (66). EDTA is a chelator of various ions, including calcium. In a prospective, randomized, multicenter trial, 122 surgical ICU patients requiring ventilation were treated with either the original formulation of propofol or the modified formulation containing EDTA. The EDTA-containing formulation had no effect on calcium or magnesium homeostasis, renal function, or sedation efficacy compared with the original formulation. Of interest was the finding that patients receiving the EDTA formulation had a significantly lower mortality rate at 7 and 28 days than those receiving the original formulation, although this study was not designed to evaluate mortality as a primary end point (67). Other potential effects of EDTA also relate to the ability of this compound to bind cations. The EDTA-containing formulation of propofol increases excretion of zinc, which can diminish the inflammatory response to stress by decreasing the release of cytokines involved in inflammation, such as tumor necrosis factor, and generation of free radicals and other oxidants. However, the implications of these effects remain to be determined (67, 68).

A generic formulation of propofol has recently become available in the United States. The major differences between the products are that the generic formulation contains a different preservative, sodium metabisulfite (0.025%), and has a lower pH (4.5–6.4) to maintain antibacterial activity of the sulfite than does the EDTA formulation (0.005%), pH (7.0–8.5).

Tests conducted by Redhead et al. (69) compared characteristics of the two formulations of propofol. Overall, important differences were found between them, both with respect to physicochemical characteristics and antimicrobial effectiveness. In one test, samples of each formulation were subjected to excessive shaking, a well-known test of emulsion stability. After 2 hrs of shaking the generic formulation, the particle-size distribution of droplets had changed, and further changes were observed after an additional 8 hrs of shaking. In contrast, propofol with EDTA underwent no changes with 16 hrs of shaking. In a test of stability, the samples were left exposed to air for up to 48 hrs. The generic product underwent a pH change of from 6.3 to 4.2 and turned to a yellow color, and degradation products were found by chemical analysis. Propofol with EDTA maintained a constant pH and appearance, and no degradation products were detected. Propofol with EDTA slows the growth for at least 24 hrs of a wide range of microorganisms, including those most likely to be found in a hospital. In this study, the effect of the two formulations on killing of a wide range of microorganisms was tested. None of the microorganisms grew by more than 1.0 log unit in 24 hrs in the EDTA emulsion, whereas, in the generic product, one strain each of *Escherichia coli* and *Candida albicans* grew by more than 1.0 log units in the same time frame. Despite these differences, the FDA considers the two formulations to be bioequivalent and interchangeable (i.e., AB rated).

Haloperidol

Haloperidol, a butyrophenone neuroleptic drug, is the agent of choice for treatment of delirium in critically ill patients. Clinical effects are observed within 30–60 mins after iv administration and last for as long as 4–8 hrs. The usual starting dosage is 2–10 mg iv, repeated every 2–4 hrs (14). Most patients being treated for ICU delirium require much larger doses of the drug than noncritically-ill patients (11). Haloperidol does not cause major respiratory depression. The drug blocks dopaminergic transmission at postsynaptic receptor sites in the central nervous system. Patients treated with haloperidol generally seem to be more calm and are better able to make appropriate responses (70).

The adverse effects associated with haloperidol include occasional hypotension resulting from the α-blocking properties of the drug. Although rare with iv administration, haloperidol may cause extrapyramidal effects such as drowsiness, lethargy, a fixed stare, rigidity, and akathisia. These symptoms are usually mild and reversible with discontinuation of the drug (6, 71). High doses of the drug are associated with QT interval prolongation and development of torsades de pointes. The QT interval should be monitored closely, and administration of haloperidol should be discontinued if the QT interval is prolonged by more than 25% or is >450 msecs (35). Rarely, a patient may experience neuroleptic malignant syndrome, a rare complication of haloperidol therapy with a mortality rate of 20% to 30%. Neuroleptic malignant syndrome develops slowly over 24–72 hrs and can last for up to 10 days after discontinuation of the drug (72).

Dexmedetomidine

Dexmedetomidine, a selective α-2 adrenergic receptor agonist, exhibits sympatholytic, sedative, and analgesic effects, and is eight times more potent for α-2 receptor than clonidine. The drug has been approved by the FDA as a short-term sedative (<24 hrs) and analgesic in the critical care setting, specifically for use in the early postoperative period (38).

Dexmedetomidine acts at two adrenergic sites. On the one hand, the drug works by presynaptic activation of the α-2 adrenoceptor, thereby inhibiting the release of norepinephrine and terminating the propagation of pain signals. Also, by

postsynaptic activation of these receptors in the central nervous system, dexmedetomidine inhibits sympathetic activity with a resultant decrease in blood pressure and heart rate. Together, these two effects can produce sedation, anxiolysis, sympatholysis, and analgesia (73).

Dexmedetomidine has several advantages for use as a sedative in the ICU. Because the drug does not cause respiratory depression, a patient can be extubated without prior discontinuation. Because a dexmedetomidine infusion can be continued during the postextubation period, the drug provides flexibility in the timing of extubation and may be useful during the weaning process. Another advantage of the drug is easy arousability of treated patients—i.e., they can be calmly and easily awakened (38). The adverse effects of dexmedetomidine include hypotension, hypertension (with the loading dose), and bradycardia (74).

Two randomized, double-blind, parallel, placebo-controlled, multicenter studies evaluated the safety and efficacy of dexmedetomidine in mechanically ventilated patients. The starting dose and maintenance infusion were titrated to achieve mild sedation with arousal to verbal commands. In both studies, approximately 60% of patients in the dexmedetomidine group required no additional sedation. There were reductions in the need for supplemental propofol and midazolam of sevenfold and fourfold, respectively, compared with placebo recipients. In addition, dexmedetomidine reduced the requirement for morphine by 50% in both studies (38). Dexmedetomidine may lack amnestic properties, however, inasmuch as a small number of patients who received the drug recalled their ICU stay and found the experience very stressful (73). Because elimination is primarily hepatic, doses should be decreased in patients with hepatic dysfunction. Pharmacodynamic responses may be altered in the presence of both hepatic and renal dysfunction, although no dose adjustment is needed in renal dysfunction (74).

Although promising as a sedative agent with analgesic-sparing properties in the ICU, dexmedetomidine needs to be studied further with respect to its properties as a sedative and its side-effect profile, including studies longer than 24 hrs. For example, the amnestic properties of the drug need to be better elucidated. Also, inappropriate use of dexmedetomidine might induce or aggravate cardiac conduction defects or lower cardiac output (38). Appropriate patient selection is of the greatest importance, as the hemodynamic status of a patient may increase the likelihood of adverse effects. ICU patients who have hypovolemia, bradycardia, or low cardiac output should not be treated with dexmedetomidine (37). Although dexmedetomidine may be initiated with a loading infusion over 10–20 mins, therapy in some patients may begin with a maintenance infusion that is then titrated to the desired effect. Dexmedetomidine is a promising agent with multiple actions that reduces analgesic and other sedative requirements and produces a cooperatively sedated patient. Proper patient selection may reduce the incidence of adverse drug events.

MANAGING SEDATIVE AGENTS IN COMMON ICU SETTINGS

The choice of a sedative for intubation, maintenance of ventilation, and extubation profoundly influences outcome, both in terms of the patient and the economic impact. Not all patients are candidates for a single sedative agent, and clinicians are faced with numerous choices when deciding which sedative is appropriate for an individual patient. Older agents, such as the benzodiazepines, are often the sedative of choice; but in recent years, many new sedatives have become available and they need to be thoroughly understood in clinical settings.

Sedation in Cardiac Postsurgical Patients

The introduction of economic constraints has encouraged the minimization of postoperative intensive care. This minimization has stimulated interest in early extubation or "fast track" anesthesia after cardiac surgery. Because many critical care nursing standards now require a 1:1 nurse-patient ratio for newly ventilated postoperative patients, early extubation may reduce nursing requirements or allow the patient to be transported to less intensive care areas (75).

The choice of a sedative in this patient population is a major determinant of outcome. The appropriate agent would have rapid onset of action, speed and ease of dose titration, rapid recovery from sedation with fast weaning and short time to extubation, hemodynamic stability during maintenance of sedation, and control of stress responses while maintaining adrenocortical responsivity to adrenocorticotropic hormone stimulation. Two early studies by Grounds et al. (50) and McMurray et al. (54) compared sedation with propofol and midazolam in 160 patients who had undergone coronary artery bypass surgery (CABS). The results of the trial indicated that propofol permitted a significantly faster time to extubation than the other sedatives studied (Figs. 1 and 2).

In another study by Roekaerts et al. (76), continuous infusions of midazolam and propofol were compared after coronary artery surgery in 30 patients who underwent deep sedation for a mean of 9 to 10 hrs. There was no difference in the quality of sedation between the two treatment groups, but patients treated with propofol had a faster recovery from deep sedation and faster weaning from the ventilator. Ostermann et al. (30) recently published a systematic review of randomized trials comparing sedatives in the ICU setting. Of eight trials that examined the relative effectiveness of propofol and midazolam for time to extubation in postcardiac surgery patients, five found that this time was shorter for propofol than for midazolam.

Two large, prospective, randomized studies compared the efficacy and safety of early and conventional extubation. Cheng et al. (77) conducted a prospective, randomized, controlled clinical trial, evaluating morbidity outcomes and safety of a modified anesthetic technique to provide shorter sedation and earlier extubation times (1–6 hrs) than those of a conventional anesthetic protocol used for prolonged sedation and extubation (12–22 hrs) in 120 patients after CABS. This trial demonstrated that early tracheal extubation is safe in this patient population and does not increase perioperative cardiac, respiratory, hemodynamic, or sympathoadrenal morbidity. The postextubation intrapulmonary shunt fraction was improved, and both the ICU and hospital LOS were reduced (Fig. 3).

In the early extubation group, anesthesia induction consisted of 15 μg/kg fentanyl ± 50 mg thiopental. Anesthesia was maintained with isoflurane before surgery. A propofol infusion at 2–6 mg/kg/hr was commenced at the start of surgery and maintained until 1–4 hrs in the ICU. In the conventional extubation group, anesthesia induction consisted of 50 μg/kg fentanyl. A 0.1-mg/kg injection of midazolam was administered in the

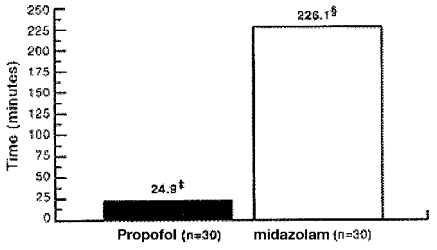

Figure 3. Time to tracheal extubation in 30 patients sedated with propofol and 30 patients treated with midazolam who received mechanical ventilation in an intensive care unit after cardiac surgery. ‡Range 5–7; §range 80–610; $p < .001$.

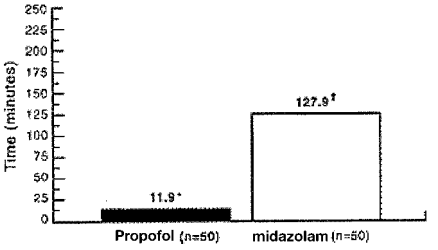

Figure 4. Time to tracheal extubation in 50 patients sedated with propofol and 50 patients treated with midazolam who received mechanical ventilation in an intensive care unit after coronary revascularization. ‡Range 2.9–19.1; §range 73.6–208.5; $p < .001$.

prebypass period. Isoflurane was used as required during the perisurgical period. In the ICU, routine infusions of morphine (2–10 mg/hr) and midazolam (1–3 mg/hr) were adjusted to achieve the same degree of sedation as in the early extubation group. Fifty-one of the 60 patients in each group (85%) were extubated within the defined time period. Postoperative extubation time and ICU and hospital lengths of stay were significantly shorter in the early extubation group. At 48 hrs after operation, no significant difference was found between the two groups in postoperative myocardial ischemia incidence and ischemia burden, creatine kinase-MB levels, plasma catecholamine (all within the normal clinical range), and ventilatory morbidity. Postextubation apnea characteristics and incidences and degree of atelectasis were similar between the groups. Intrapulmonary shunt fraction improved significantly in the early group at 4 hrs after extubation. There was a similar incidence of treated postoperative complications in the two groups, but three patients in the conventional extubation group died of stroke or postoperative myocardial infarction (77).

In another randomized controlled trial conducted by the same investigators, the costs of therapy for early and late extubation, and the time parameters for ICU and hospital stay, were compared in patients after CABS. Early extubation significantly reduced the cost of coronary ICU stay by 53% ($p < .026$) and the total cost of CABS by 25% ($p < .019$) when compared with late extubation. In each group, 41 of 50 patients (82%) were extubated within the defined period, and both the ICU LOS and the overall hospital LOS were significantly lower for the early extubation group ($p = .046$ and $p = .015$, respectively) (78) (Fig. 4).

Because late extubation and conventional anesthesia for CABS are well-established practices, the major modifications required for early extubation should be thoroughly evaluated and should include postoperative intensive care management. Through the use of an appropriate anesthetic technique and postoperative management, Silbert et al. (75) demonstrated that early extubation can be achieved after CABS without major complications. In a prospective, randomized, controlled trial, 100 patients undergoing elective CABS were randomized to early extubation or conventional extubation. Those in the early extubation group received a reduced dose of fentanyl (15 mg/kg) and an anesthetic compatible with early extubation, whereas those randomized to conventional extubation received fentanyl at a dose of 50 mg/kg. In the early extubation group, anesthesia was augmented by administration of propofol for induction and maintenance. The median time to extubation in the early extubation group (240 mins) was significantly less than that in the conventional extubation group (420 mins) ($p < .01$). Importantly, early extubation did not result in an increased rate of reintubation, postoperative myocardial infarction, or other complications. The authors noted that, besides demonstrating that early extubation is as safe as conventional extubation, there are several theoretical advantages of the technique, including earlier mobilization of the patient, decreased risk of nosocomial infection, better pulmonary function and improved hemodynamics. They pointed out, however, that it is not known if these "benefits" will prove significant in practice.

Delirium in the ICU

Delirium, a common disorder in ICU patients, has often been referred to as "ICU psychosis." This term for uncontrolled agitation is, however, inappropriate and nonspecific (35). It was introduced to underline the etiological significance of psychosocial and psychological factors in understanding the syndrome (5). A more specific definition of delirium is "an acute, reversible organic mental syndrome with disorder of attention and cognitive function, increased or decreased psychomotor activity, and a disordered sleep-wake cycle." The estimated prevalence of delirium in the ICU is 15% to 40% and is escalating as a result of increases in the number of elderly and more severely ill patients admitted to the ICU. In this setting, delirium contributes to increased morbidity and is associated with a poorer prognosis and a mortality rate of 10% to 33% (79).

Delirium is a consequence of a nonspecific central nervous system reaction to disruption of the internal environment that is necessary for normal function. Predisposing factors for delirium include advanced age, underlying primary cerebral illnesses such as dementia and Alzheimer's disease, and a history of alcohol or substance abuse. Underlying chronic systemic illness accentuated by metabolic and hemodynamic instability, hypoxemia, acidosis and electrolyte imbalances, severe infections, and intracerebral abnormalities, such as brain tumors, can also precipitate delirium. ICU-related factors contributing to the development of delirium include sleep deprivation, sensory overload, lack of meaningful verbal or cognitive stimulation, and immobilization. Withdrawal of drugs such as opioids, sedatives, and several other pharmacologic agents can also contribute to the development of delirium (79). Among the more common causes of altered mental status in critically ill patients are adverse drug reactions and drug–drug interactions. Numerous drugs, including those with anticholinergic properties, cardiovascular drugs, H_2-receptor antagonists, and antimicrobials all can be responsible for mental disturbances and delirium (80).

The differential diagnosis of delirium includes dementia, depression, and schizophrenia. Dementia develops slowly and is long lasting, whereas delirium has an acute onset and recovery is almost always complete. The hypoactive form of delirium may be mistaken for depression, but disorientation, which is common in delirium, is not a feature of depression. Acutely schizophrenic patients may seem

confused, but examination reveals that they do not have cognitive deficits. In addition, schizophrenia is associated with auditory, rather than visual, hallucinations (79).

Two distinct clinical presentations of delirium have been observed. In hyperactive delirium, patients are restless and agitated; conversely, those with the hypoactive variant exhibit decreased consciousness and psychomotor activity. A mixture of hyperactive and hypoactive delirium is also seen in some patients (79). An interesting characteristic of delirium is that the behavior of the patient can change dramatically within hours or even minutes. Drowsiness and lethargy can change to alertness and lucidity for a time, and then can quickly change to agitation and aggression (81).

The delirious patient sometimes incorrectly perceives the environment as hostile or threatening. The patient may attempt to escape, necessitating the use of physical or chemical restraints, or may try to assault staff and visitors. There is also an increased risk of self-harm resulting from unintentional dislodgment of critical life-support and monitoring equipment. Such a situation often prolongs the length of an ICU stay, necessitates further invasive treatment, and increases the risk of additional complications. Also important to note is that, because of the impairment of short-term memory associated with delirium, a patient may not even remember an episode of delirium once it has subsided (79).

If a patient exhibits unsafe behavior, insomnia, hallucinations, delusions, agitation, or psychomotor hyperactivity, pharmacologic therapy should be considered (14). In most ICUs, a neuroleptic agent is the recommended medication for treatment of delirium resulting from causes other than withdrawal. Haloperidol is generally the neuroleptic agent of choice because, in addition to its efficacy, this drug has few anticholinergic and hypotensive effects. Other agents that are often used to sedate patients and enhance sleep—including benzodiazepines, antihistamines, and hypnotics—usually worsen delirium (81). Nevertheless, benzodiazepines are occasionally given in combination with haloperidol, which allows for the use of smaller and safer dosages of either agent alone (79). Doses of medications used to treat a patient's primary condition should be reduced or discontinued if they contribute to delirium. If the drug cannot be discontinued, a change to a similar drug with less risk of delirium is advisable. Analgesics should also be given if the patient is experiencing pain. Patients with delirium related to alcohol or drug withdrawal may continue to be delirious even when their withdrawal symptoms are being adequately treated. In these situations, neuroleptic agents should be added to the medications specified in a withdrawal protocol (81).

Respiratory Failure and Patient-Ventilator Asynchrony

Patients undergoing mechanical ventilation are likely to breathe out of synchronization with the ventilator when agitation resulting from fear and anxiety causes tachypnea (26). Changes in the patient's respiratory status and the development of asynchrony between the patient and the ventilator may also represent a possible emergency situation. "Fighting" or "bucking" the ventilator describes the presence of agitation and respiratory distress in the ventilated patient. Because agitation leads to an increase in CO_2 and lactic acid production, life-threatening respiratory and metabolic acidosis may occur. This desynchronization between efforts of inspiration and their rhythm with the ventilator can result in ineffective oxygen delivery and CO_2 elimination. Some of the signs of respiratory distress are tachypnea, diaphoresis, and cardiovascular abnormalities (82).

There are numerous possible causes of sudden respiratory distress. Ventilator-related causes include improper setting of the ventilator and malfunctions of the equipment. Causes related to the airway include malposition of the endotracheal tube, cuff problems, endotracheal obstruction, and airway trauma from tracheostomy tubes. Patient-ventilator asynchrony may be caused by inappropriate ventilator selection or settings, inadequate F_{IO_2} or positive end-expiratory pressure level, and ventilatory rate. Finally, causes related to the patient include abnormalities in the airway, lung parenchyma, and pleural space, as well as cardiovascular dysfunction and altered ventilatory drive (83).

Appropriate sedation is especially important in patients with respiratory failure. When sufficient doses are administered, sedatives can diminish patient struggle against mechanically supported breaths, improve chest wall compliance, and allow manipulation of inspiratory to expiratory ratio and other ventilator variables to maximize oxygenation (84). If hypoxia caused by circulatory failure is the indication for mechanical ventilation, propofol or midazolam, which can affect systemic vascular resistance, should be carefully and slowly titrated. Respiratory failure developing from other causes of hypoxia is not exacerbated in the sedated patient if care is taken to insure proper ventilation with appropriate delivery of oxygen concentration. In addition to its sedative properties, propofol, in contrast to other agents used for sedation, may be beneficial to patients with severe air flow obstruction; studies have demonstrated that this agent reduces pulmonary resistance in ventilated chronic obstructive lung disease patients (26).

Sedation During Weaning from Mechanical Ventilation

Managing agitation and pain in mechanically ventilated patients who are ready for weaning requires a thorough understanding of the available pharmacologic agents, because their manifestations can profoundly influence the outcome of weaning. It is now well known that patients being weaned from mechanical ventilation require appropriate sedation for a successful outcome with respect to extubation and release from the ICU. The stresses of the ICU environment, including bright or flashing lights, alarms, hectic pace, and exposure to unfamiliar personnel, often lead to anxiety and agitation. In addition, sleep disruption, undergoing numerous tests and procedures, immobility for extended time periods, and physical restraints all further necessitate the need for sedation (71).

Nonpharmacologic intervention at the time of weaning may relieve mild anxiety. Such interventions include changing the environment, using relaxation techniques, reassuring the patient, and providing adequate rest and psychological support. However, for patients who do not respond to these interventions, pharmacologic therapy should be instituted, and sedatives should be given on a regularly scheduled basis to promote stable blood levels (71).

Agents that can contribute to significant respiratory depression should be avoided when a patient is being weaned from mechanical ventilation. Opioids and benzodiazepines should not be used or, if

the patient is already being treated with these agents, they should be discontinued or reduced during the weaning process. However, because patients often become more highly anxious during weaning, there is a real need for sedation. Haloperidol, a neuroleptic, is often employed during the weaning process because it does not produce respiratory depression. Propofol is another useful drug for sedation during the weaning process because, compared with benzodiazepines, it has a quick onset and short duration of action, thereby reducing the time needed for recovery of spontaneous respiration (85).

Several studies have attempted cost-benefit analyses by comparing propofol and midazolam for sedation in patients receiving mechanical ventilation in the ICU. In a study by Carrasco et al. (61), critically ill patients were allocated to receive short-term (7 days) continuous sedation with either midazolam or propofol. Propofol was more expensive than midazolam, but there was a cost savings of approximately $18 per patient in the propofol group that was attributable to a shorter ICU stay. Barrientos-Vega et al. (59), in an open-label, randomized, prospective trial, compared the effectiveness of sedation, time required for weaning, and costs of prolonged sedation of critically ill patients undergoing mechanical ventilation for more than 24 hrs with midazolam or propofol. Midazolam and propofol were equally effective as sedative agents. Despite large differences in the cost of the two agents for sedation, the economic profile was more favorable for propofol than for midazolam because of the shorter weaning time for patients receiving propofol. On average, the midazolam group required >4 days to awaken and wean from mechanical ventilatory support once the infusion was terminated, whereas the propofol group averaged 35 hrs ($p < .0001$).

In a multicenter, randomized, open-label trial, Hall et al. (51) compared propofol and midazolam, given for different durations of time, on extubation time and LOS in the ICU in 99 evaluable critically ill patients (53 in the midazolam group and 46 in the propofol group) in four different types of ICUs. After admission to the ICU, physicians assessed whether patients would require sedation for short-term (≤24 hrs), medium-term (>24 hrs and <72 hrs), or long-term (≥72 hrs) mechanical ventilation. The dose of each drug was adjusted to achieve a daily-targeted Ramsay Sedation Scale score. Sedation with propofol was associated with a shorter time to tracheal extubation than sedation with midazolam, but there was either no difference in the time to ICU discharge or a prolonged time for the propofol group. The authors speculated that this difference with respect to time to discharge from the ICU might be accounted for by a delay in patient transfer secondary to systematic handling of the patients or, alternatively, patients in the propofol group may have required more ICU care for other critical illnesses.

Walder et al. (86) conducted a systematic review of 27 randomized trials to establish the efficacy and harm of propofol vs. midazolam in mechanically ventilated patients. In 13 trials, mostly postoperative, sedation lasted from 4 to 35 hrs. In nine of these trials, the average weaning time from ventilation was 0.8–4.3 hrs with propofol and 1.5–7.2 hrs with midazolam. There was a relatively shorter weaning time with propofol in six trials and with midazolam in one trial; in one trial, the time was equivalent for the two drugs. Across all trials, the adequacy of sedation with propofol was longer than with midazolam. The authors suggested that propofol, because of its rapid redistribution compared with midazolam, may be advantageous when frequent dose adjustments are required, such as in agitated patients. There was also strong evidence that weaning times were shorter after sedation for ≤36 hrs with propofol.

In an interesting approach to improving on the sedative effects of both midazolam and propofol, and to take advantage of the best features of each drug, studies have been conducted to evaluate their combined use. The interaction between propofol and midazolam is synergistic rather than simply additive, as demonstrated in a prospective, controlled, randomized, double-blind trial conducted by Carrasco et al (61). The combination of the two agents was compared with each agent alone in post-CABS patients. Combined therapy was equally as effective as either agent alone and was associated with rapid awakening and extubation, reduction in overall sedative dosage, and resultant lower pharmaceutical acquisition cost. This study highlights an interesting and potentially useful drug interaction between midazolam and propofol and offers a promising area of investigation for future studies of ICU sedation (27).

USING SEDATIVE AGENTS IN SPECIAL ICU CIRCUMSTANCES

The care of patients in the ICU is highly challenging, not least because of differences between patients that can significantly affect the outcome of management. Age, personal characteristics, underlying disease, and the nature of the insult leading to admission to the ICU all profoundly affect the decision-making process for patient management. Sedation is a key part of treatment in the ICU; patients adapt more easily to intubation and mechanical ventilation when they receive the appropriate sedative and pain medication. Sedation must be individualized to the patient. Benzodiazepines may be appropriate for one patient, whereas propofol may be preferred for another. Following is a discussion of some of the special groups of patients who require a specific approach to sedation—alcohol and drug abusers experiencing withdrawal symptoms when confined to the ICU, patients with status asthmaticus, patients undergoing end-of-life terminal weaning, pregnant women, patients undergoing endotracheal intubation, and traumatic head injury patients.

Many critically ill patients fall into special clinical situations that must be taken into consideration when instituting sedation. The critical care practitioner is frequently challenged in the ICU by the inability to quickly and easily diagnose situations, such as drug or alcohol withdrawal, that may interfere with the induction of sedation. Withdrawal syndromes in individuals with a history of heavy alcohol and benzodiazepine use have historically been associated with high rates of morbidity and mortality.

Alcohol Withdrawal

Delirium tremens is the most serious manifestation of the alcohol withdrawal spectrum. It is seen in approximately 5% of hospitalized patients with a history of alcohol abuse, and has a mortality rate ranging from 1% to 15% (64). Withdrawal symptoms can progress over a period of 24–72 hrs to delirium tremens, a condition marked by agitation, tremor, and an acute state of confusion associated with disorientation, hallucinations, and autonomic hyperactivity. Whenever possible, treatment of alcohol withdrawal should be initiated before the onset of agitated delirium. Patients with worsening conditions and those with concomi-

tant medical problems require admission to the ICU. Here, control of seizures, maintenance of hemodynamic stability, arrhythmia management, airway protection, and correction of nutritional and metabolic deficiencies are facilitated with initiation of pharmacologic therapy for withdrawal (37).

Once heavy alcohol use has been identified, proper prophylaxis should be instituted, both by maintaining optimal electrolyte levels through potassium, magnesium and phosphorous replacement, and by administration of thiamine, vitamin B_{12}, and folate together with an appropriate sedative. The most important pharmacologic treatment is use of agents that are cross-tolerant with alcohol, thereby providing prophylaxis against seizures and relieving the frequently intense agitation, hallucinosis, and tremulousness. Although treatment with alcohol is effective and can be intravenously titrated, such treatment is not addressed in most reviews and has not been well studied in clinical trials. The short duration of action of ethanol requires prolonged administration and does not always eliminate the need for additional therapy. The most widely administered pharmacologic agents for the treatment of alcohol withdrawal are benzodiazepines (37).

Alcohol ingestion affects many regulatory systems; among the consequences are an increase in the release of endogenous opiates, activation of the GABA-A receptor, inhibition of the *N*-methyl-D-aspartate (NMDA) receptor, and interactions with serotonin and dopamine receptors. Chronic exposure to the inhibitory GABA-A and excitatory NMDA receptors is believed to play a role in the pathogenesis of alcohol withdrawal. The long-term effects of alcohol on the number and function of central nervous system receptors cause excessive central nervous system excitability during periods of abstinence, resulting in the signs and symptoms of delirium tremens (87).

Treating alcohol withdrawal usually includes the substitution of an agent with effects on the GABA-A receptor. Because benzodiazepines potentiate this neurotransmitter, they have been successfully used to reduce the signs and symptoms of withdrawal. Barbiturates are not recommended because they have a narrow therapeutic index, and haloperidol is less effective in preventing delirium and seizures. Propofol may be an alternative to benzodiazepines for controlling alcohol withdrawal symptoms, but there is limited data available supporting its use in nonintubated patients (35).

With the exception of a few case reports, there have been limited studies of propofol for treatment of patients with delirium tremens in the ICU setting (87, 88). There are, however, several properties of propofol, including less cross-tolerance than traditional benzodiazepines, ease of titratability, and a rapid metabolic clearance, that make it a promising drug for sedation in patients with severe alcohol withdrawal and delirium tremens. Like alcohol, propofol affects both the GABA-A and glutamate receptors (87).

Other Withdrawal and Intoxication Syndromes

Another complicating factor in the management of ICU patients is the presence of symptoms related to either the withdrawal of drugs or drug intoxication resulting from adverse effects, or drug–drug interactions. These symptoms may arise with drugs used therapeutically in the ICU, or with licit or illicit drugs that the patient used before hospital admission.

Withdrawal syndromes are a frequent occurrence in the ICU, especially in urban locations, because 36% of intentional injury victims are drug-dependent. Withdrawal syndromes confuse the clinical management of such patients and may be extremely difficult to diagnose. These syndromes are often lethal, and prophylactic measures should be taken to prevent their emergence in all patients identified at risk. Therefore, it is safe to consider all ICU patients to be at high risk for drug or alcohol dependence unless proven otherwise. Where there is doubt, patients should be tested for evidence of drugs and interviewed together with family members for the presence of drug- dependence traits. Appropriate patients should be referred for formal evaluation and treatment once they have been stabilized. Withdrawal syndromes must be promptly recognized, differentiated from traumatic or metabolic deterioration, and treated. The mainstay of most withdrawal therapy is supportive care and treatment with the appropriate sedative (i.e., benzodiazepines or propofol). In consideration of the high rate of multiple intoxicants present in trauma patients, withdrawal can occur from multiple agents in a single patient, further compounding the difficulties inherent in managing this patient population (81).

Withdrawal from benzodiazepines in the ICU includes an abstinence syndrome, which is marked by anxiety, fear, confusion, and agitation. In addition, the possibility of tachycardia and panic attacks may occur as the patient emerges from sedation. Severe withdrawal symptoms, including refractory seizures, may be seen when benzodiazepines are discontinued in critically ill patients who had been receiving treatment with these agents before their hospital admission. Treatment with a benzodiazepine such as oral lorazepam is appropriate for abstinence or withdrawal symptoms, with slow tapering of the dose. Intravenous agents such as lorazepam or midazolam can be used in intubated patients. Clonidine and beta-adrenergic blockers can be administered to modify symptoms and improve tolerance to benzodiazepine withdrawal (89).

Narcotic withdrawal is common in patients receiving long-term therapy with opioids for palliative care of cancer or chronic pain syndromes, as well as in patients with a history of narcotic abuse. Replacement of the narcotic with continuous infusions of fentanyl or morphine sulfate, or administration of methadone, is commonly used in the ICU.

Cocaine, a sympathetic-stimulating drug, increases the release of presynaptic norepinephrine and blocks its reuptake. This action causes various cardiopulmonary and neuropsychiatric effects including tachycardia, hypertension, respiratory depression, anxiety, tremor, seizures, and hyperthermia (90). When initiating sedation in patients who are in a hypercatecholaminic state, it is important to determine both the patient's history of cocaine use and evidence of withdrawal symptoms. Benzodiazepines are commonly used for sedation of patients with suspected or known cocaine abuse and, although propofol has occasionally been administered, its use for sedation of cocaine abusers is not strongly supported in the literature. The hypercatecholamine state must also be treated in these patients; both α- and β-blockers have been used successfully. In addition, all patients suspected of a withdrawal syndrome should be rapidly evaluated for other physiologic causes such as hypoxemia, hypercarbia, or electrolyte abnormalities.

Padula and Willey (91) examined the hypothesis that smokers undergoing

forced abstinence from tobacco in a cardiac ICU would be more anxious than nonsmoking patients and exhibit more withdrawal symptoms. There were 16 smokers and 17 nonsmokers enrolled in the study. The investigators evaluated two types of anxiety, state anxiety (a measure of situational anxiety) and trait anxiety (a measure of general anxiety). The presence of withdrawal symptoms was based on patient perception of increased heart rate, degree of calmness, and degree of restlessness. The results of the study indicated that smokers exhibited significantly higher trait anxiety compared with nonsmokers, but there was no difference in state anxiety between the groups. Neither group reported physical withdrawal symptoms, but smokers experienced more psychological withdrawal symptoms than nonsmokers on the first day after admission. Reversal of symptoms can be achieved by using nicotine patches, which are commonly used in patients with multiple traumas.

Status Asthmaticus

Patients presenting with status asthmaticus, or severe asthma that is unresponsive to standard therapy, usually require mechanical ventilation and sedation until respiratory function improves. Benzodiazepines are the most commonly used sedative in these patients. Propofol may be most appropriate for asthmatic patients inasmuch as it has recently been shown to have substantial bronchodilatory properties at high doses not demonstrated with other sedatives or analgesics (26). These bronchodilatory properties were demonstrated in a study showing that propofol reduces pulmonary resistance (decreases in airway resistance and intrinsic positive end-expiratory pressure) in patients with chronic obstructive pulmonary disease who were undergoing mechanical ventilation (92). Other clinical studies have shown a similar effect of propofol in patients with chronic obstructive pulmonary disease (93). Propofol containing EDTA is commonly used in patients at risk of status asthmaticus for its bronchodilatory properties and its lack of a trigger in extrinsic asthma or in patients with sulfite intolerance (26).

Benzodiazepines have no intrinsic bronchodilating properties, and prolonged effects from continuous infusion of these agents have been associated with an increase in complications as well as prolonged ventilator use, ICU and hospital stays. Other agents with bronchodilator properties such as ketamine and halothane have undesirable side effects (93). A potential problem with the use of propofol is that high doses are required to elicit a smooth muscle relaxant effect, raising concern about hypotension as an adverse effect. Little is known about whether bronchodilation occurs at standard doses of the drug. However, in patients undergoing mechanical ventilation who are showing high peak pressures and severe bronchospasm, the use of propofol in addition to standard therapy for bronchospasm may have additional benefits.

Terminal Weaning. In recent years, there has been a greater awareness of the importance of providing maximum comfort to terminally ill patients who are being weaned from mechanical ventilation. In this context, patient comfort is directly related to the choice of sedative.

The management of patients undergoing end-of-life care in the ICU includes, in many cases, terminal weaning from mechanical ventilation. Of prime importance is that critical care practitioners provide quality end-of-life care. Once the patient, the family, and the primary-care physician have made the decision, the attending physicians in the ICU are responsible for providing the patient a comfortable, anxiety-free withdrawal from mechanical ventilation.

When a decision to forgo treatment is made, the focus should be on specifying the goals of patient care and assessing treatments in light of these goals. The use of appropriate palliative measures can nearly always control symptoms accompanying withdrawal of life support. After ICU interventions are discontinued, patient comfort becomes the most important objective. This must be assessed frequently, and signs of discomfort should be treated with adequate doses of sedatives and opioids. If terminal weaning is chosen, a limited time course should be agreed on to prevent prolongation of the dying process (94).

Dyspnea and anxiety should be anticipated when ventilator support is withdrawn. Opioids and benzodiazepines or propofol have become the drugs of choice to treat dyspnea and anxiety or agitation, respectively. These agents should be immediately available and titrated to effect, but may also be given before ventilator withdrawal to prevent anticipated symptoms and signs of distress from occurring. There is wide variation in the doses required to relieve symptoms because of previous drug exposure, level of tolerance, drug metabolism, and degree of awareness. Occasionally, opioid-tolerant patients require higher doses of morphine (94). When choosing a sedative, it is necessary to balance the beneficial effects in terms of patient comfort with possible toxic effects that may adversely affect the respiratory or cardiovascular state of the patient, thereby increasing the discomfort level and possibly causing premature death.

Wilson et al. (95) conducted a study to determine why and how sedatives and analgesics are ordered and administered during the withholding and withdrawal of life support. In a total of 22 critically ill patients from each of two ICUs, they found that large doses of sedatives and analgesics were ordered primarily for relief of pain and suffering during the withholding and withdrawal of life support, and that the time to death was not decreased by drug administration. The study found that, after the initiation of the withholding or withdrawal of life support, the median time until death was 3.5 hrs in patients receiving drugs and 1.3 hrs in those not receiving drugs. The reasons for drug administration were to decrease pain (88% of patients), anxiety (85% of patients), and air hunger (76% of patients); to comfort families (82% of patients); and to hasten death (39%), although hastening death was never the only reason cited. Not surprisingly, significantly lower amounts of benzodiazepines and opiates were given in the 24 hrs before withholding and withdrawal of life support than were given after withdrawal was initiated.

In a Canadian retrospective cohort study, Hall et al. (96) compared the use of sedation and pain relief to prevent and treat discomfort during the dying process in the end-of-life care of ICU patients who were or were not withdrawn from life support. In the final 12 hrs of life, there was a wide variability (greater than tenfold) among physicians in the two ICUs studied with respect to prescribed doses of morphine and sedative agents, whether or not life support was withheld or withdrawn. Diazepam and midazolam were used more frequently than lorazepam or propofol. Doses of morphine and lorazepam were fivefold higher in patients from whom life support was withdrawn in comparison with patients for whom life support was continued. The amount of morphine used in patients withdrawn

from life support increased over the 12-hr period and particularly in the final 4 hrs of life. Similar results were noted for the use of lorazepam, midazolam, and propofol.

Pregnancy

Although opioids are known to cross the placenta and have an effect on neonatal outcome, there is also evidence that both propofol and the benzodiazepines can crossover to the fetus. Therefore, it is important that these drugs be titrated to appropriate levels when used to sedate the pregnant patient in the ICU. With respect to teratogenicity, although it is known that long-term opioid use affects intelligence and other neurologic factors in neonates, there is little evidence for such effects with propofol.

It has been reported that several clinical trials have evaluated the effect of propofol and other sedatives or anesthetics on pregnancy outcome in women undergoing an assisted reproductive technique. In a multicenter retrospective pilot trial and survey, Beilin et al. (97) evaluated the effect of sedatives and anesthetics on pregnancy outcome after gamete intrafallopian transfer, a type of assisted reproductive technique usually performed laparoscopically under general anesthesia. Participating in the survey were seven US fertility clinics representing 455 procedures. The clinical pregnancy rate (number of pregnancies/number of procedures) was 35% and the delivery rate (number of women who delivered at least one live baby/total number of procedures) was 32%. There was no statistical difference in either rate between women who received a sedative or anesthetic (propofol, nitrous oxide, midazolam, or isoflurane) and those who did not. Two other clinical studies evaluated the effect of propofol on outcome in women undergoing assisted reproductive technology. In these studies, as in the study by Beilen et al., the effect of propofol on oocytes was evaluated, and no deleterious effect was found. In another study, in which propofol had a negative effect on pregnancy rate, the effect of the drug on embryos, rather than oocytes, was evaluated.

Endotracheal Intubation

In the ICU, a key aspect of endotracheal intubation of the patient with failing respiratory status is the ability to make the patient comfortable rapidly while managing the airway. When choosing the most appropriate sedative agent for this purpose, the hemodynamic stability and volume status of the patient must be considered. Propofol is an appropriate agent if the volume status of the patient is acceptable and the patient is not hypovolemic. In patients who are hemodynamically unstable, however, etomidate is commonly used since it has fewer vasodilatory and myocardial depressant effects in critically ill patients than do other sedative agents. Midazolam, thiopental, or methohexital are not used because they can cause hypotension.

Head Trauma

Patients with head injuries present a challenge in the ICU that differs from trauma without central neurologic involvement. The aim of therapy is to ameliorate the effects of the initial injury while preventing secondary injury such as edema, infection, and ischemia. Patients with head trauma should always be monitored by means of neurologic examination. The confusion and agitation resulting from brain injury often cause the patient to struggle and resist nursing care and mechanical ventilation. Because intracranial hypertension is a frequent occurrence, the effects of sedatives on cerebral metabolism and intracranial elastance must be considered before use in this patient population (37). Elevated intracranial pressure (ICP) is the most important pathophysiology resulting from head injury. An increase in ICP decreases the cerebral perfusion pressure (CPP), which is the driving force behind cerebral blood flow. Thus, patients with head injury experience reduced cerebral blood flow (25).

Head injury produces multiple systemic effects that must be considered in patient management. For example, hypotension is common after injury to the hypothalamus, brain stem, or spinal cord, so that ablation of the remaining sympathetic drive with pharmacologic sedation may lead to sudden and occasionally severe cardiovascular collapse, which leads to further brain ischemia. Alternatively, a frequently observed hyperadrenergic state requires that sedation provide protection from additional stress, yet not risk the critical care standard of maintaining organ perfusion. Therefore, before treating with sedatives, it is essential to evaluate the volume status and hemodynamic reserve of the patient (37).

It is of critical importance that the ventilated patient with head trauma be easily and quickly awakened on a periodic basis for neurologic evaluation. After physiologic abnormalities have been evaluated, the degree of discomfort should be addressed, because pain aggravates the stress response, leading to further increases in ICP. Opioids relieve pain and alleviate the hyperadrenergic state by providing analgesia and sedation, and these agents normally do not perturb intracranial dynamics when ventilation is controlled. A disadvantage of the use of opioids is that these drugs may cloud the neurologic evaluation. Other limiting effects of opioid sedation are the potential for gastrointestinal hypomotility and the delay of the weaning process and successful extubation (37).

The aims of treatment for patients with head injury are reduction and/or maintenance of ICP within acceptable ranges, maintenance of adequate CPP, and minimization of brain activity. Mechanical ventilation and drug therapy are used to accomplish these aims. Administration of sedative agents is an integral part of the management scheme (all sedatives cause cerebral depression to some extent). The ideal sedative reduces ICP while maintaining an adequate CPP. Another property of an ideal sedative for patients with head injuries is titratability management with diuretics and antihypertensive agents that may affect intravascular volume. Benzodiazepines have been commonly used in this setting, with midazolam being the drug of choice because of its short half-life, but this agent may exhibit a prolonged duration of sedation in patients receiving continuous infusions for 24 hrs or longer, with emergence delayed for 1–2 days or longer (25).

Continuous infusions of both propofol and remi-fentanyl are beneficial because both are short acting. Propofol is safe in patients with severe head injuries, is easily titratable, and reduces ICP. In addition, propofol decreases cerebral metabolic rate while having little effect on CPP reduction. Because of propofol's extremely short half-life, it is possible to arouse the patient in order to conduct a thorough neurologic examination, and consequently decrease both the number of serial CT scans and the associated cost (25).

Kelly et al. (98) conducted a multicenter, double-blind trial in 42 intubated patients with head trauma in which continuous infusion of 2% propofol was compared with a regimen of morphine sulfate. Mean daily ICP and cerebral perfusion pressure were generally similar between groups until the third day of therapy, when ICP was significantly lower in the propofol group compared with the morphine group ($p < .05$). Patients treated with propofol required significantly less use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and cerebrospinal fluid drainage compared with patients treated with morphine ($p < .05$). A favorable outcome, defined as good recovery or moderate disability, was observed 6 months postinjury in 52% of patients receiving propofol and in 47% receiving morphine, whereas the mortality rates were 17% and 21%, respectively. The best outcomes were achieved in patients receiving the highest doses of propofol for the longest duration. The authors noted that, despite a higher incidence of poor prognostic indicators in the propofol group, propofol-based sedation, together with an ICP control regimen, is safe, acceptable, and is possibly a desirable alternative to opioid-based sedation regimens in this patient population.

In another study (99), propofol was evaluated in 10 patients with severe head injuries who were undergoing mechanical ventilation. The rate of infusion of the drug was adjusted to maintain the ICP at <10 mm Hg and CPP at 60 mm Hg. Propofol was discontinued after 24 hrs. There were no significant differences in mean arterial pressure, but mean CPP tended to increase during the study. Overall, the quality of sedation was determined to be good in nine patients. In a study by Pearson et al. of hemodynamically stable head trauma patients, propofol and morphine were compared for their effects on ICP and CPP. ICP was similar in both treatment groups. In patients treated with propofol, CPP increased slightly over 48 hrs, whereas there was a slight decrease in CPP in patients receiving morphine. The observed decrease in ICP and increase in CPP with propofol is consistent with the majority of reports from other clinical trials and in the literature.

QUESTIONS AND ANSWERS FROM AGITATION ROUNDTABLE MEETING

Question

Dr. Cohen: It has been said that if you cannot measure it, you cannot manage it. An argument could be made that acute respiratory distress syndrome management has improved a great deal because of the availability of better monitoring systems such as pulse oximetry. Along this line of reasoning, what should we be looking for in the way of future monitoring tools to help fine-tune our approach to handling agitation in the ICU?

Answer

Dr. Gallagher: To date, the BIS monitor has been used to measure anesthetic depth in the operating room. In the ICU, BIS may only be useful in the paralyzed patient—one that requires titration to some sedation level. In nonparalyzed patients, we tend to titrate to a clinical level—this can result in variable and continually changing BIS levels—depending on the degree of stimulation. There are others in my group that have not yet found it very useful, however; we still require better, more objective monitoring of patient sedation and anxiety levels.

Another factor is an easily reproducible sedation scoring system. For instance, with the Ramsey scale, the terminology goes back and forth between an exam and patient activity, and can be easily misinterpreted.

We use a *modified*, modified Ramsay scale that everyone in our unit understands and interprets exactly the same way. This has significantly improved sedation titration and communication between staff. Staff consensus regarding sedation scale selection or adaptation is very important.

Anne Pohlman: The key to all monitoring devices or assessment tools is the ability for all individuals using the devices to communicate the information gained in a reliable and efficient manner.

Dr. Gallagher: The simpler the scale, the easier it is to reproduce. This makes it much more likely to be used and understood by everybody in the unit.

Anne Pohlman: One other piece of equipment that is beginning to surface in the ICU by way of our "Sleep" colleagues is portable polysomnography equipment. As discussed earlier, the role of sleep in the ICU is only beginning to be investigated in detail. Important to remember when discussing new equipment or new technology, is our ability to incorporate it into bedside practice in a manner that assists the staff in caring for the patient to improve outcomes.

Question

Dr. Cohen: Based on the known evidence, what advice do you offer about room lighting pattern, visiting hours, and timing of nursing activities to prevent or treat agitation?

Answer

Anne Pohlman: Control of environmental factors such as noise, lighting, room temperature, and around-the-clock stimulation from staff is clearly important in the treatment of agitated patients, but to date have not been studied or proven to change outcomes in acutely ill patients. Studies are underway to look at the relationship of these variables in both the chronic and acute critically ill patient in the ICU.

Dr. Papadakos: My personal opinion is that sleep becomes extremely important in the later stages of an illness. As an example, when you have a patient that is difficult to wean off the ventilator, a regular sleep-wake cycle goes a long way toward orienting the patient and facilitates weaning.

Dr. Gallagher: The patient who is sleep-deprived is probably much more difficult to wean, but I do not think this association has been well studied. We try to keep patients who are weaning off the ventilator comfortable because weaning requires a large amount of work, and a rested patient is a better candidate to be weaned.

Prof. Dasta: I think there is some immune response activity to sleep and maybe wound healing relative to physiologic sleep. So, if there are ways of mimicking physiologic sleep, that would be a good attribute.

Question

Dr. Cohen: Anne, would you comment on how much literature there is to support this information. What do you believe to be profitable areas for future research into the topic of environmental manipulation and its impact on outcome?

Answer

Anne Pohlman: There is not much literature available with respect to environment changes in the ICU. The components of the environment that have been studied include excessive noise, abnormal light/dark cycles, and frequent care-related activities. These studies have told us what many of us in the critical care world already know: it is noisy, bright, and patients do not get much uninterrupted time while in the ICU. The effectiveness of sleep-promoting strategies needs to be demonstrated, recognizing the difficulty and complexity of doing this type of study in the ICU. There are a few studies in the procedure areas addressing interventions such as music therapy, massage therapy, and therapeutic touch. The direct effect of these maneuvers on acutely ill patients remains undetermined. Controlling the environment in the ICU for noise, light, and temperature is an ongoing challenge, as many older ICUs do not have options for modifying temperature, light and noise, nor can bedside staff regulate them. Newer pumps, bedside monitors, and ventilators allow bedside clinicians to set volume and tone alarms to decrease noise. Recent ICU room and unit designs allow for natural light from windows, and for artificial lighting to be directed and controlled from wall dimmer switches. Portable unit-specific phones have recently been added to the ICU environment; these phones are tied into the call light system and the pager system set to vibrate rather than ring thus eliminating the need for unit intercoms.

Question

Dr. Cohen: Does anyone have any polices or rules and regulations governing environmental management for agitation in their ICUs?

Answer

Anne Pohlman: I have not seen any hospital policies or rules regulating any of these specific environmental concerns. However, in the 15 yrs that I have been an ICU nurse, we have changed dramatically the policy regarding visiting hours and family involvement in care. Unit-specific environmental changes may include rescheduling tasks that interrupt sleep such as baths in the middle of the night, 4 a.m. daily chest x-rays, and scheduled line changes during off hours. Potentially, these tasks could be "batched" into single time periods rather than occurring as continuous stimulation around the clock. Combining these tasks would depend of course on patient acuity, staffing patterns, and medical staff availability for procedures. With multidisciplinary "buy in," it seems a study looking at these issues may be possible.

Question

Dr. Cohen: Do any of the other panelists feel that study of environmental management would be a worthwhile area of investigation?

Answer

Dr. Papadakos: Yes, obviously, but measuring the impact of those variables is going to be very, very difficult. There have been several studies in anesthesia trying to put music headphones on the patients during anesthesia and trying to measure whether or not that affects how the patient feels afterward. But I think it makes empirical sense that a very calm, soft environment is a lot better than a noisy, loud, bright environment. You would also have to look at the color on the walls and the view outside of the window. My entire surgical ICU overlooks the cemetery.

Anne Pohlman: Other ICU environmental issues such as encouraging family support and addressing psychosocial needs of patients is imperative when dealing with agitated patients. In a recently published paper by Hupcey [Hupcey JE: Feeling safe: The psychosocial needs of ICU patients. *J Nurs Scholarsh* 2000; 32: 361–367], it was reported that the overwhelming need of ICU patients was to feel safe. Family and friends, ICU staff, religious beliefs, and feelings of knowing, regaining control, hoping, and trusting all influenced the perception of feeling safe. Altering the ICU environment to foster communication and address individual patient/family needs during curative interventions or comfort-care strategies is imperative.

Dr. Gallagher: Visitors are a two-edged sword. We have fairly liberal visiting hours, but I do not think we pay enough attention to who is visiting. Some visitors tend to help and others make things worse. This is a very difficult issue to grasp. It is a problem.

Question

Dr. Cohen: Translating knowledge into action is a serious concern in health care. What is our status in the area of using pharmacologic agents for agitation management? Is there a problem, and what are its causes?

Answer

Prof. Dasta: In the Hansen-Flaschen et al. article in *JAMA* in 1991 [Hansen-Flaschen JH, Brazinsky S, Basile C, et al: Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. *JAMA* 1991; 266: 2870–2875], head nurses of pulmonary ICUs were asked what kinds of drugs were used in their facilities. They reported that a wide variety of drugs were being employed, and this awakened us to the problem of polypharmacy in the agitated patients. And I am not sure that the current state of affairs is that much better today, although I believe that guideline development with multidisciplinary input does add an evidence-based approach to what we do—if it is followed.

We surveyed this practice in our surgical ICU and published our results in 1994. On average, our patients received two drugs. The range was zero to nine—one patient received nine different drugs for agitation or pain. Overall we documented 23 different drugs in more than 200 patients.

We tend to throw things at patients without optimizing any single strategy, for instance adding a sedative while the patient's pain is not properly controlled.

With respect to our understanding of the metabolism and excretion of various agents, we certainly know more about them today than we did 10 yrs ago, but we know about the kinetics and dynamics in isolation, with monotherapy. What I do not think we fully understand is the dynamics and kinetics of lorazepam, for example, in the patient who is also receiving morphine and haloperidol, and also diphenhydramine. So, the complex pharmacology in the real world is poorly understood.

Understanding what the various drugs do and what they do not do remains an issue. It is not unusual to find a patient receiving a neuromuscular blocker by infusion and not having a drug that has amnestic properties on board. Or to see a PRN morphine order in a patient receiv-

ing a neuromuscular blocker. Such oversights indicate a basic gap in understanding.

Anne Pohlman: The ability to change practice based on research or evidence-based medicine continues to be an ongoing challenge. Using our own sedation "wake up" study as an example, when the study was completed and daily "wake up" assessments directed by the research team stopped—within a very short period of time the recent practice change of daily "wake up" assessments stopped as well. Fostering the practice change through a multidisciplinary approach in which there is "buy in" from all bedside caregivers was required. In our unit, sedation "wake up" assessments are now a part of shift-to-shift report and daily rounds.

Prof. Dasta: That is a really good point. Another issue is the long-term psychological effects of sedatives. This is an area we need to learn more about. In *Critical Care Medicine* this past year, a study by Nelson et al. (100) showed a correlation between the number of days of sedation and the development of depression as well as post-traumatic stress disorder symptoms.

Question

Dr. Cohen: Withdrawing sedatives after prolonged use frequently is an arduous endeavor peppered by PRN sedative doses and increasing drip rates. Because delirium is a likely occurrence in the awakening amnestic patient, what is the role for antipsychotic agents/haloperidol in combination with sedative agents? And how early should we be starting these antipsychotic agents?

Answer

Dr. Abraham: Yes, and we touched on the use of haloperidol earlier in this discussion. This is actually a very complicated question. The sedative agents often cause disorientation, particularly the benzodiazepines, in critically ill patients, in the elderly patients, or in patients who have multiple organ system dysfunction. Haloperidol is probably preferred in this situation and should probably be instituted at an earlier point. Ventilator-dependent patients, as their respiratory status is improving, are prone to having sleep disorders and confusion, even post-extubation. Getting a handle on their delirium at an early point with haloperidol is probably a good idea.

Dr. Papadakos: I think one of the other things that you have to consider is withdrawal of opioids. As the associate director of a burn trauma unit, I can tell you that we have a big problem trying to wean people off long-term, high-dose opioids. We have had some success using methadone.

Dr. Abraham: Yes, and in the same way I think patients who are on benzodiazepines often develop tachyphylaxis, and so decreasing those agents contributes to increased agitation as well.

Question

Dr. Cohen: What do you recommend for sleep in the delirious patient for whom you are trying to minimize the use of sedating agents?

Answer

Dr. Papadakos: We have done some work looking at increasing levels of propofol at night and then titrating it off in patients who are sleep deprived. We have used drugs such as diphenhydramine and some of the other commonly prescribed sleep medications in patients who are not intubated or on mechanical ventilation. We do use some of the sleep medications that the elderly commonly take, such as diphenhydramine, alprazolam, and shorter-acting benzodiazepines. Many elderly patients have trouble sleeping and are on drugs at home. We try to replicate these regimens orally or via the feeding tube. I do not know if other people on the panel use these agents in their intensive care unit.

Prof. Dasta: We occasionally use diphenhydramine, with caution in the elderly because of the anticholinergic properties that it might have. I know I take it when I am on an airplane and I want to sleep.

Question

Dr. Cohen: From a pathophysiological perspective, what do you believe are the most common errors made in the prevention or treatment of agitation?

Answer

Dr. Gallagher: I think there are two. First is failure to recognize pain. Second (especially in a training institution where multiple people are writing orders) everybody has a favorite or preferred drug to use for the agitated patient. Usually the patient ends up on a variety of agents. As I stated earlier, once you get involved with multiple drugs, the situation becomes confused and very difficult to sort out. So, I recommend simplicity in selection and using only one agent at a time.

Question

Dr. Cohen: One of the principles of total quality management is that reduction of variation leads to improvement in quality. In the past, regulatory standards have forbidden the use of standardized protocol approaches to the use of restraints. It sounds like the requirements for restraining agitated patients are now getting more onerous. Is this antiprotocol sentiment still the case, and how do we deal with this counter-intuitive policy?

Answer

Anne Pohlman: The regulatory standards regarding the use of restraints have been revised again in 2001. Institution-specific policies and guidelines required to meet these revised standards can be onerous. The bottom line with the use of restraints remains unchanged; patient safety is a priority and we, as healthcare providers, need to optimize our treatment strategies to assure safety without merely turning to restraints and tying patients down. So, in essence, as a bedside practitioner, my goal—like the regulatory standard—is patient safety. The onerous part for us at the bedside is developing guidelines that describe our practice of ensuring safety in the ICU. For example, (1 standardizing patient assessment tools; (2 instituting patient-specific interventions that ensure patient safety (this may include the use of restraints if necessary, however other less restrictive measures should be initiated first); (3 scheduling frequent reassessment practices; and, of course, (4 documentation strategies that confirm that this practice is being carried out.

Dr. Cohen: It is my impression from past reading of JCAHO literature that they expressly forbid the use of protocols.

Anne Pohlman: JCAHO forbids the use of protocols if it is a protocol that does not take individual patient needs into account. For example, a protocol that states that all mechanically ventilated patients require restraints while in the ICU is not

acceptable. However, a protocol stating that patients in the ICU requiring mechanical ventilation will be reassessed frequently for level of consciousness and tolerance to the current therapies and interventions is acceptable. Other items to consider in the protocol include suggested interventions to reorient the patient and optimize safety with regard to invasive catheters and interventions. If restraints are required, they are applied to ensure patient safety, *not* staff convenience.

Dr. Cohen: Can you use a protocol providing that the standard is met with adequate documentation?

Anne Pohlman: Exactly. What they are really looking for is an assessment of what was going on, what you did, and what follow-up measures were taken. They want to ensure that we are not just randomly putting patients in restraints.

Dr. Gallagher: We have a protocol that works fairly well. An intubated patient in the ICU essentially meets the protocol. When the JCAHO came through the last time they were reasonably happy with that approach.

Question

Dr. Cohen: About the risk of withdrawal from analgesics and sedatives, can you comment on which agents, if any, present significant risk, and on the impact of duration and intensity of therapy?

Answer

Prof. Dasta: Opioid and benzodiazepine withdrawal after a week or more of therapy presents particular problems. Maybe one way of addressing the problem is a progressive tapering or a systematic tapering of therapy during the ICU stay. The daily awakening approach that Anne has used at her institution may also minimize the risk of withdrawal.

Question

Dr. Cohen: Does anybody rotate or change drug groups to try to avoid the risk of withdrawal?

Answer

Multiple Responses: No.

Dr. Abraham: The important thing is to try to judge when the patient needs to be off the drug, and start some weaning process in advance of that—maybe several days, because the longer you go, the longer, obviously, it is going to take. But that works much better than trying to change drugs.

Anne Pohlman: The addition of the oral agents, for example, oral lorazepam, may help while the infusions are titrated off slowly. We need to also remember that many of these patients may have been taking medications like the benzodiazepines for anxiety before being hospitalized as well.

Dr. Papadakos: I think I mentioned that looking at the patient's home medications is important. As you pointed out, many of the elderly are on either psychiatric medications or sleep medications at home, and trying to replicate those is key.

Question

Dr. Cohen: Would you briefly describe one or two examples (not necessarily about agitation) of approaches to reducing the evidence-care gap and minimizing variation that work in your critical care unit? By evidence-care gap, I mean something that has been shown to work well in the research setting, but its not being used well in practice.

Answer

Dr. Abraham: I think the best example of this is probably ventilator therapies for adult respiratory distress syndrome (ARDS). At the American Thoracic Society annual meeting, there was a fascinating abstract from Gordon Rubenfeld looking at utilization of low tidal volume ventilation at the University of Washington (along with our institution, one of ten of the NIH ARDS network centers). Before the results showing a substantial benefit were published in the *New England Journal of Medicine*, about 5% of the patients were managed with low tidal volume, since the *New England Journal* paper appeared, about 8% are managed appropriately!

So, there is the issue about dissemination of clinical management criteria and utilization of these algorithms. What we have done is institute protocols in the medical and surgical ICU for patients with acute lung injury and ensured that the respiratory therapists are aware of both the protocols and which patients are at risk, and will actually follow up with the radiologist to find out if the patients do, indeed, have acute lung injury. The directors of the units have signed on to this plan. The teams managing the patients have to make an active decision for those patients not to be managed by the NIH protocol. We, like the University of Washington and a lot of other people, were disappointed by voluntary assumption of these kinds of new clinical practice patterns.

I believe that an institutional protocol is probably the best approach. As we discussed with sedation, whenever one institutes a protocol and standardizes therapy, there are multiple potential benefits.

Dr. Cohen: I think that 5% to 8% indicates just how big a problem this really is.

Dr. Abraham: Yes, it is tremendous; in a condition with a clear-cut 25% reduction in mortality, and with publication of a lead article in a major journal. Finally, there has been a lot of talking about it. Everybody says that they do manage their patients with low tidal volume ventilation, but the evidence says otherwise.

Dr. Papadakos: I think the availability of protocol order sheets that eliminate physician variability is very important. That is what we've instituted at our institution. The sedation protocol is actually an order check box in the patient's chart. In teaching hospitals, this may be more difficult because of the number of people involved.

We try to remove original thought from the process and do the same thing with ventilator management. A low tidal volume protocol has been used at the University of Rochester for almost 12 yrs. It is on a standardized order sheet, so there are not a lot of choices for the residents or other staff members to make.

I wonder if supporting orders–you know, protocolized orders—are probably more important than having protocols.

Anne Pohlman: Holding all staff accountable to the practice change is important. Making change a part of patient management is optimal. For example, in the case of low tidal volume ventilation, the respiratory therapist ensures compliance with ventilator settings during routine ventilator checks. This way we have multiple checks and balances within the system—physician orders, bedside monitoring by nurses, and respiratory therapy vent checks—all making sure that the right strategy is in place.

Dr. Gallagher: I do not know that I necessarily agree with protocols to the extent that boxes are "checked off," particularly in a training institution. This approach can diminish the trainees' abilities to think. When they get to a situa-

tion that does not match up, they can become lost and are unable to deal with it properly. I do not think having the protocol is wrong; the issue is whether you review the patient's course so that people can learn also by their mistakes. It may be a lot easier to run a protocol in the private setting, especially if just a few individuals are involved in overseeing the day-to-day management. In my experience, to achieve multiple goals in a training institution, dealing with protocols is a lot harder and takes a lot more energy.

Question

Dr. Cohen: Do you have any way of providing feedback for clinicians about their compliance? As you said, everybody thinks they are doing a wonderful job. Do you have any way of saying "your compliance with this protocol is 50%"; is there any tracking?

Answer

Dr. Abraham: Yes, for example, with the ventilated protocol, we do not do it on an individual basis, because people find that a bit too threatening, but we do it on a divisional basis. Division members who attend in the ICU, for example, will be made aware of these statistics. In our experience, the drivers for these changes in practice are actually the fellows far more than the faculty. The fellows and residents are much more modifiable in terms of their behavior patterns. And so we also disseminate this information to the house staff, both our own fellows and the medicine house staff who are in the unit. The surgeons and collaborators do the same thing.

Question

Dr. Cohen: A large number of people use alternative therapies on a regular basis in the outpatient setting. Can you comment on the use of herbal medications, acupuncture, melatonin, acupressure massage, etc., in the ICU?

Answer

Dr. Papadakos: Fortuitously, I was recently at the European meeting of anesthesiology in Florence, and I did attend a small satellite session on the use of herbal medications. Many clinicians have a very low understanding of the pharmacologic effects of many herbal medications.

We now know about the drug–drug interaction of some commonly used herbal medications in our society. I think it is important for us, before we start using these drugs, to develop an understanding of how they work. Educating healthcare providers in how these drugs work is a necessary first step.

Other alternative therapies (acupuncture and acupressure), are commonly used in the critical care settings in hospitals in the Orient. I have rounded on an intensive care unit in China, and I can tell you that acupuncture is used commonly and successfully in patients for management of pain and reduction of anxiety. But again, the same level of expertise does not exist in Western medicine.

Overall, I think more and more people are using herbal medications and herbal teas, and I think there is a growing interest to educate physicians in the interaction of herbal therapies and traditional pharmacologic agents.

REFERENCES

1. Covington H: Use of propofol for sedation in the ICU. *Crit Care Nurse* 1998; 18:34–39
2. 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
3. *Deleted in proof*
4. Wise MG, Cassem NH: Behavioral disturbances. *In:* Critical Care. Third Edition. Civetta JM, Taylor RW, Kirby RR (Eds). Philadelphia, Lippincott-Raven, 1997, pp 2017–2029
5. Crippen D, Ermakov S: Stress, agitation, and brain failure in critical care medicine. *Crit Care Nurs Q* 1992; 15:52–74
6. Harvey M: Managing agitation in critically ill patients. *Am J Crit Care* 1996; 5:7–15
7. Haskell RM, Frankel HL, Rotondo MF. Agitation. *AACN Clin Issues* 1997; 3:335–350
8. Sessler CN, Grap MJ, Brophy GM: Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001; 22:211–225
9. Levine RL: Pharmacology of intravenous sedatives and opioids in critically ill patients. *Crit Care Clin* 1994; 10:709–731
10. Jenkins DH: Substance abuse and withdrawal in the intensive care unit: Contemporary issues. *Surg Clin North Am* 2000; 80:1033–1053
11. Hassan E, Fontaine DK, Nearman HS: Therapeutic considerations in the management of agitated or delirious critically ill patients. *Pharmacotherapy* 1998; 18:113–129
12. Crippen DW: The role of sedation in the ICU patient with pain and agitation. *Crit Care Clin* 1990; 6:369–392
13. DeJonghe B, Cook D, Appere-De-Veechi C, et al: Using and understanding sedation scoring systems: A systematic review. *Intensive Care Med* 2000; 26:275–285
14. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615
15. Hansen-Flashen J, Cowen J, Palomano 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
16. Devlin JW, Boleski G, Mlynarek M, et al: Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999; 27:1271–1275
17. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–1379
18. Riker RR, Fraser GL: Monitoring sedation, agitation, analgesia, neuromuscular blockade, and delirium in adult ICU patients. *Semin Respir Crit Care Med* 2001; 22: 189–198
19. Gan TJ, Glass PS, Windsor A, et al: Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; 87:808–815
20. Kearse LA Jr, Rosow C, Zaslavsky A, et al: Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. *Anesthesiology* 1998; 88:25–34
21. Weinart CR, Chlan L, Gross C: Sedating critically ill patients: factors affecting nurses' delivery of sedative therapy. *Am J Crit Care* 2001; 10:156–167
22. Cooper AB, Gabor JY, Hanly PJ: Sleep in the critically ill patient. *Semin Respir Crit Care Med* 2001; 22:153–163
23. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342: 1471–1477
24. Joint Commission on Accreditation of Healthcare Organizations (JCAHO): *Comprehensive Accreditation Manual for Long Term Care*. Standards and Intents for Sedation and Anesthesia Care. Revisions to Anesthesia Care Standards, effective January 1, 2001
25. Hooper VD, George-Gay B: Sedation in the critically ill patient. *Crit Care Nurs Clin North Am* 1997; 9:395–410
26. Mazzeo AJ: Sedation for the mechanically ventilated patient. *Crit Care Clin* 1995; 11: 937–955
27. Young C, Knudsen N, Hilton A, et al: Sedation in the intensive care unit. *Crit Care Med* 2000; 28:854–866
28. Mascia MF, Koch M, Medicis JJ, et al: Phar-

macoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care. *Crit Care Med* 2000; 28: 2300–2306
29. Doyle DJ: Propofol: A synopsis of its pharmacology and clinical uses in the OR and ICU. Available at: http://doyle.ibme.utoronto.ca/propofol/. Accessed May 23, 2001
30. Ostermann ME, Keenan SP, Seiferling RA, et al: Sedation in the intensive care unit: A systematic review. *JAMA* 2000; 283: 1451–1459
31. Spencer L, Willatts S: Sedation. *In:* Textbook of Intensive Care. Goldhill D, Withington S (Eds). London, Chapman & Hall, 1997, pp 95–101
32. American College of Critical Care Medicine, American Society of Health-System Pharmacists, American College of Chest Physicians: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119–141
33. Mascia MF, Koch M, Medicis JJ, et al: Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care. *Crit Care Med* 2000; 28: 2300–2306
34. Devlin JW, Holbrook AM, Fuller HD: The effect of ICU sedation guidelines and pharmacist interventions on clinical outcomes and drug cost. *Ann Pharmacother* 1997; 31:689–695
35. Jacobi J, Farrington EA: Supportive care of the critically ill patient. *In:* Pharmacotherapy Self-Assessment Program (PSAP). Third Edition. Kansas City, MO: The American College of Clinical Pharmacy; 1999, pp 129–151
36. Wagner BKJ, O'Hara DA: Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet* 1997; 33:425–453
37. Mirski MA, Muffelman B, Ulatowski JA, et al: Sedation for the critically ill neurologic patient. *Crit Care Med* 1995; 23:2038–2053
38. Shapiro BA, Warren J, Egol AB, et al: 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
39. Nasraway SA: Use of sedative medications in the intensive care unit. *Semin Respir Crit Care Med* 2001; 22:165–174
40. Watling SM, Dasta JF, Seidl EC: Sedatives, analgesics and paralytics in the ICU. *Ann Pharmacother* 1997; 31:148–153
41. Shafer A: Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med* 1998; 26:947–956
42. Cawley MJ: Short-term lorazepam infusion and concern for propylene glycol toxicity: Case report and review. *Pharmacotherapy* 2001; 21:1140–1144
43. Lown KS, Thummel KE, Benedict PE, et al: The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther* 1995; 57:16–24
44. Pohlman AS, Simpson KP, Hall JB: Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: A prospective, randomized study. *Crit Care Med* 1994; 22: 1241–1247
45. Mirenda J, Broyles J: Propofol as used for sedation in the ICU. *Chest* 1995; 108: 539–548
46. Cremer OL, Moons KGM, Bouman EAC, et al: Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117–118
47. Aitkenhead AR, Willatts SM, Park GR, et al: Comparison of propofol and midazolam for sedation in critically ill patients. *Lancet* 1989; 2:704–709
48. Carrasco G, Cabre L, Sobrepere G, et al: Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting. *Crit Care Med* 1998; 26:844–851
49. Chamorro C, de Latorre FJ, Montero A, et al: Comparative study of propofol versus midazolam in the sedation of critically ill patients: Results of a prospective, randomized, multicenter trial. *Crit Care Med* 1996; 24:932–939
50. Grounds RM, Lalor JM, Lumley J, et al: Propofol infusion for sedation in the intensive care unit: preliminary report. *BMJ* 1987; 294:397–400
51. Hall RI, Sandham D, Cardinal P, et al: Propofol vs midazolam for ICU sedation: A Canadian multicenter randomized trial. *Chest* 2001; 119:1151–1159
52. Higgins TL, Yared J-P, Estafanous FG, et al: Propofol versus midazolam for intensive care unit sedation after coronary bypass grafting. *Crit Care Med* 1994; 22:1415–1423
53. Kress JP, O'Conner MF, Pohlman AS, et al: Sedation of critically ill patients during mechanical ventilation: A comparison of propofol and midazolam. *Am J Respir Crit Care Med* 1996; 153:1012–1018
54. McMurray TJ, Collier PS, Carson IW, et al: Propofol sedation after open heart surgery: A clinical and pharmacokinetic study. *Anaesthesia* 1990; 45:322–326
55. Roekaerts PMHJ, Huygen FJPM, de Lange S: Infusion of propofol versus midazolam for sedation in the intensive care unit following coronary artery surgery. *J Cardiothorac Vasc Anesth* 1993; 7:142–147
56. Ronan KP, Gallagher TJ, George B, et al: Comparison of propofol and midazolam for sedation in intensive care unit patients. *Crit Care Med* 1995; 23:286–293
57. Sanchez-Izquierdo-Riera JA, Caballero-Cubedo RE, Perez-Vela JL, et al: Propofol versus midazolam: Safety and efficacy for sedating the severe trauma patient. *Anesth Analg* 1998; 86:1219–1224
58. Sandiumenge Camps A, Sanchez-Izquierdo Riera JA, Vasquez DT, et al: Midazolam and 2% propofol in long-term sedation of traumatized, critically ill patients: Efficacy and safety comparison. *Crit Care Med* 2000; 28: 3612–3619
59. Barrientos-Vega R, Sanchez-Soria MM, Morales-Garcia C, et al: Prolonged sedation of critically ill patients with midazolam or propofol: Impact on weaning and costs. *Crit Care Med* 1997; 25:33–44
60. Barrientos-Vega R, Sanchez-Soria M, Morales-Garcia C, et al: Pharmacoeconomic assessment of propofol 2% used for prolonged sedation. *Crit Care Med* 2001; 29:317–322
61. Carrasco G, Molina R, Costa J, et al: Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients: A cost-benefit analysis. *Chest* 1993; 103: 557–564
62. *Deleted in proof*
63. Ewart MC, Yau KW, Morgan M: 2% propofol for sedation in the intensive care unit: A feasibility study. *Anesthesia* 1992; 47: 146–148
64. McLeod G, Dick J, Wallis C, et al: Propofol 2% in critically ill patients: Effect on lipids. *Crit Care Med* 1997; 25:1976–1981
65. Bennett SN, McNeil MM, Bland LA, et al: Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; 333:147–154
66. Thompson KA, Goodale DB: The recent development of propofol (DIPRIVAN®). *Intensive Care Med* 2000; 26:S400–S404
67. Herr DL, Kelly K, Hall JB, et al: Safety and efficacy of propofol with EDTA when used for sedation of surgical intensive care unit patients. *Intensive Care Med* 2000; 26: S452–S462
68. Higgins TL, Murray M, Kett DH, et al: Trace element homeostasis during continuous sedation with propofol containing EDTA versus other sedatives in critically ill patients. *Intensive Care Med* 2000; 26:S413–S421
69. Redhead HM, Jones CB, Bobey DG: Pharmaceutical and antimicrobial differences between propofol emulsion products [letter]. *Am J Health Syst Pharm* 2000; 57: 1174–1175
70. Nejman AM: Sedation and paralysis. *In:* Critical Care. Third Edition. Civetta JM, Taylor RW, Kirby RR (Eds). Philadelphia, Lippincott-Raven, 1997, pp 821–835
71. Carroll K, Magruder K: The role of analgesics and sedatives in the management of pain and agitation during weaning from mechanical ventilation. *Crit Care Nurs Q* 1993; 15:68–77
72. Lund N, Papadakos PJ: Barbiturates, neuroleptics, and propofol for sedation. *Crit Care Clin* 1995; 11:875–886
73. Gertler R, Cleighton Brown H, Mitchell DH, et al: Dexmedetomidine: A novel sedative-analgesic agent. *BUMC Proc* 2001; 14:13–21
74. Bhana N, Goa KL, McClellan KJ: Dexmedetomidine. *Drugs* 2000; 59:263–268
75. Silbert BS, Santamaria JD, O'Brien JL, and The Fast Track Cardiac Care Team: Early

extubation following coronary artery bypass surgery: A prospective randomized controlled trial. *Chest* 1998; 113:1481–1488
76. Roekaerts PMHJ, Huygen FJPM, de Lange S: Infusion of propofol versus midazolam for sedation in the intensive care unit following coronary artery surgery. *J Cardiothorac Vasc Anesth* 1993; 7:142–147
77. Cheng DCH, Karski J, Peniston C, et al: Morbidity outcome in early versus conventional tracheal extubation after coronary artery bypass grafting: A prospective randomized controlled trial. *J Thorac Cardiovasc Surg* 1996; 112:755–764
78. Cheng DCH, Karski J, Peniston C, et al: Early tracheal extubation after coronary artery bypass graft surgery reduces costs and improves resource use: A prospective, randomized, controlled trial. *Anesthesiology* 1996; 85:1300–1310
79. Roberts BL: Managing delirium in adult intensive care patients. *Crit Care Nurse* 2001; 21:48–54
80. Fish DN: Treatment of delirium in the critically ill patient. *Clin Pharm* 1991; 10: 456–66
81. Justic M: Does "ICU psychosis" really exist? *Crit Care Nurse* 2000; 20:28–37
82. Yagan MB, White D, Stabb J: Sedation of the mechanically ventilated patient. *Crit Care Nurs Q* 2000; 22:90–100
83. Hess DR, Kacmarek RM: Pharmacologic therapy: Sedatives, analgesics, and paralytic agents. *In*: Essentials of Mechanical Ventilation. Hess DR, Kacmarek RM (Eds). New York, McGraw Hill, 1996, pp 207–214
84. Valente JF, Anderson GL, Branson RD, et al: Disadvantages of prolonged propofol sedation in the critical care unit. *Crit Care Med* 1994; 22:710–712
85. Dattani D, Wong G: Intensive care unit sedation: Agents used to sedate agitated ICU patients. Available at: http://www.pharmacyconnects.com/content/; hppractice/1996/01–96/f04_features.html. Accessed August 4, 2001
86. Walder B, Elia N, Henzi I, et al: A lack of evidence of superiority of propofol versus midazolam for sedation in mechanically ventilated critically ill patients: A qualitative and quantitative systematic review. *Anesth Analg* 2001; 92:975–983
87. McCowen C, Marik P: Refractory delirium tremens treated with propofol: A case series. *Crit Care Med* 2000 6:1781–1784
88. Coomes TR, Smith SW: Successful use of propofol in refractory delirium tremens. *Ann Emerg Med* 1997; 30:825–828
89. Durbin CG Jr: Sedation of the agitated, critically ill patient without an artificial airway. *Crit Care Clin* 1995; 11:913–936
90. Brody SL, Slovis CM, Wrenn KD: Cocaine-related medical problems: Consecutive series of 233 patients. *Am J Med* 1990; 88: 325–331
91. Padula C, Willey C: Tobacco withdrawal in CCU patients. *Dimens Crit Care Nurs* 1993; 12:305–312
92. Conti G, Dell'Utri D, Vilardi V, et al: Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. *Acta Anaethesiol Scand* 1993; 37:105–109
93. Zaloga GP, Todd N, Levit P, et al: Propofol-induced bronchodilation in patients with status asthmaticus. *Internet J Emerg Intensive Care Med* 2001; 5:[http://www.icaap.org/iuicode?895.1.5
94. Faber-Langendoen K, Lanken PN, for the ACP–ASIM End-of-Life Care Consensus Panel: Dying patients in the intensive care unit: Forgoing treatment, maintaining care. *Ann Intern Med* 2000; 133:886–893
95. Wilson WC, Smedira NG, Fink C, et al: Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. *JAMA* 1992; 267:949–953
96. Hall RI, Graeme M, Rocker GM: End-of-life care in the ICU: Treatments provided when life support was or was not withdrawn. *Chest* 2000; 118:1424–1430
97. Beilin Y, Bodian CA, Mukherjee T, et al: The use of propofol, nitrous oxide, or isoflurane does not affect the reproductive success rate following gamete intrafallopian transfer (GIFT): A multicenter pilot trial/survey. *Anesthesiology* 1999; 90:36–41
98. Kelly DF, Goodale DB: Williams J, et al: Propofol in the treatment of moderate and severe head injury: A randomized, prospective double-blinded pilot trial. *J Neurosurg* 1999; 90:1042–1052
99. Smith I, White PF, Nathanson M, et al: Propofol: an update on its clinical use. *Anesthesiology* 1994; 81:1005–1043
100. Nelson BJ, Weinert CR, Bury CL, et al: Intensive care unit drug use and subsequent quality of life in acute lung injury patients. *Crit Care Med* 2000; 28:3626–3630