
Sedation Therapy: Improving Safety and Quality of Care

Proceedings from
The Sixth Conference
Center for Safety and Clinical Excellence
November 17-18, 2005, San Diego, CA
Philip J. Schneider, MS, FASHP, Editor

Issues and Opportunities

Assessment of Sedation/Delirium/Pain

Sedation Management: Medications/Techniques

Administration and Monitoring: New Technologies

*Conference report published by
carefusion.com
Center for Safety and Clinical Excellence
San Diego, CA
2005*

Inter-professional Conference on Pain Management and Sedation

The sixth conference at the Center for Safety and Clinical Excellence in San Diego, held November 17-18, 2005, brought together a distinguished faculty from clinical practice, academia, organizations and government. Philip J. Schneider, MS, FASHP, Director of the Latiolais Leadership Program and Clinical Professor at The Ohio State University, chaired the conference. Nationally recognized experts from different health professions focused on current issues and opportunities in postoperative pain management and sedation in intensive care patients. This document summarizes the information presented on sedation therapy with regard to safety concerns, criteria for determining best practices, guidelines, assessment, nursing issues, and new administration and monitoring technologies that can help improve safety and quality of care. A second document summarizes the presentations and roundtable discussion of topics related to pain management and patient-controlled analgesia.

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EDITORIAL

Asleep at the Wheel

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The expression “*asleep at the wheel*” means one has fallen asleep while driving a vehicle, or “*behind the wheel*.” It can also describe someone who is blissfully unaware of a dangerous situation. As we heard and discussed the presentations at the 6th Conference of the Center for Safety and Clinical Excellence Improvement, I was struck by my own lack of awareness of the dangerous situation that seems to arise more commonly than I would have thought with the use of drugs for sedating patients. Technology that makes it possible to more closely monitor patients who are being treated with sedation medications for either procedures or agitation have shown that respiratory depression is much more common than previously thought. This is especially true in procedure areas and medical/surgical units outside the intensive care unit, where patients may be unattended for longer periods of time.

While Stoelting points out that we do not always have randomized con-

trolled studies to provide evidence for all medical practices, we do have, as Bouchard presents, a wonderful array of drugs that can be used to sedate patients. Jacobi summarizes guidelines for the safe and effective use of these medications based on the opinions of experts. Sessler describes sedation assessment scales that can be used by clinicians to monitor the patient’s response to treatment. Ramsay points out the value of using these scales to improve the use of sedatives. Maddox, Shaw, Struys, and Absalom describe existing and developing technologies for the more effective administration of these medications. Yet, we still have problems.

There may be several reasons for this. In discussing these presentations, several points were made. First, there was a debate over the importance of evidence-based medicine. Some participants felt that there needed to be randomized controlled trials before any guidelines or technologies are adopted as a standard of practice. Without standardi-

zation, variability in practice exists, which increases the chances of harm. A second issue was the current problems in the workforce. The nursing shortage was cited as one barrier to quality of care. Proper education on the use of sedatives, scales to assess the patient response, and training to use new drug administration and monitoring technologies are critical to achieving the desired outcomes.

The components to effective sedation management are available. What is missing is execution. Just like driving a car, the use of potent medications requires our full attention. A better understanding of the drugs used to sedate patients, the tools used to assess patients, and effective use of the technologies that more effectively deliver the doses of sedatives and monitor patient response is needed. The information presented at this conference and contained in these proceedings is an effective contribution to improving sedation therapy.

Issues and Opportunities in Sedation and Pain Management: Perspectives from the Anesthesia Patient Safety Foundation

Robert K. Stoelting, MD, President, APSF, Indianapolis, IN

Key Points

- *Opportunities exist to make significant changes and improvements in perioperative care that can translate into better patient care and improved patient safety.*
- *In addressing such concerns, the criteria to determine best practices for improving patient safety need to be considered.*
- *Safety changes reflect decreases in the incidence of rare events, so that randomized controlled trials to determine efficacy of interventions intended to prevent rare events are not always possible or needed to endorse new patient safety practices.*
- *Anesthesia safety was achieved by making changes that made sense, were based on an understanding of human factors principles, and had been documented to be effective in other settings.*
- *A common theme in these safety changes is they made sense and were the right thing to do.*

Although significant progress has been made in making the perioperative-period experience safer, adverse events still occur. There are still opportunities to make changes and improvements that translate into better perioperative care and improved patient safety. This conference is an opportunity to discuss safety concerns associated with postoperative pain management and sedation in the intensive care unit (ICU), and the criteria that should be used to determine best practices for improving patient safety.

Postoperative Pain Management

In the Summer 2005 issue of the Anesthesia Patient Safety Foundation (APSF) Newsletter, Frank J. Overdyk, MD, wrote that more deaths have been reported to the Food and Drug Administration with patient-controlled analgesia (PCA) than with all other intravenous infusions combined.¹ In this article, he also expressed the opinion that thousands of patients are at risk for opioid-induced depression of ventilation. It was suggested that routine

patient monitoring with pulse oximetry and capnography would prevent more than 90% of PCA-associated complications—a significant opportunity for improved patient safety. An unanswered question is who (physicians, nurses, respiratory therapists) should monitor PCA infusions?

Sedation in the ICU

Sedation in the ICU may be accomplished with multiple drugs often administered in combination with or without infusion devices. There is currently great interest in using propofol to provide sedation based on its unique pharmacokinetics (rapid onset and prompt recovery). Disadvantages of propofol include its dose-related depression of ventilation and circulation and its ability to produce general anesthesia. Concern that administration of propofol by individuals not trained in the management of anesthetized patients may result in adverse events is a controversial topic. Development of infusion devices that administer propofol based on its pharmacokinetics combined with pulse oximetry and capnography presents a potential opportunity to improve patient safety.

Achievement of Conference Goals

Achievement of the goals of this conference will depend on the application of principles shown by other organizations such as APSF to be effective in achieving improved patient safety. These principles include (1) practitioner education and dissemination of information (expert conferences, educational publications), (2) research (medical and technology), (3) industry participation and support, (4) specialty society endorsement (standards), (5) support of accrediting organizations (Joint Commission on Accreditation of Healthcare Organizations), and (6) mobilization of public opinion via the media.

Adoption of Safety Changes

An overriding question is “what criteria should be used to determine best practices for improving patient safety?”² Safety changes reflect decreases in the incidence of rare events. Controlled and randomized studies to determine efficacy of interventions intended to prevent rare events are not always possible or needed to endorse new patient safety practices. In fact, there will never be complete evidence for everything that must be done in medicine to improve patient safety. The prudent alternative to evidence-based data is to make reasonable judgments based on the best available evidence combined with successful experiences in health care.

Evidence-based Medicine

Rigorous proof of efficacy is neither necessary nor in many cases sufficient for recommending widespread use of a safety practice.² Although continued outcomes research is needed to establish and improve the scientific evidence base for medical practice, formal evidence may neither be appropriate or essential for all of the interventions needed to improve patient safety.

Aviation safety was not built on evidence that certain practices reduced the frequency of crashes. Aviation relied on widespread implementation of hundreds of small changes in procedures, equipment, training and organization that aggregated to establish a strong safety culture and effective practices. These changes made sense, were usually based on sound principles, technical theory or experience, and addressed real-life problems, but few were subjected to controlled experiments.

In health care, the progress in anesthesia safety is similar to that in aviation. The achievement of improved anesthesia patient safety is not attributable to a single practice or development of new anesthetic drugs or even any type of improvement (such as technological advances) but to application of a broad array of changes in process, equipment, organization, supervision, training, and teamwork.² No single one of these changes has been

proven to have a clear-cut impact on mortality. Anesthesia safety was achieved by applying many changes that made sense, were based on an understanding of human factors principles, and had been shown to be effective in other settings. A common theme in all these safety changes is they made sense and were the right thing to do. To say that convincing evidence of progress and effect is lacking because randomized trials of all safe anesthesia practices have not been conducted would be counterproductive.

Summary

Development and ultimate achievement of the safety opportunities in postoperative pain management and sedation in the ICU will require persistence and patience. It is critical to recognize that evidence-based data are not necessary for instituting patient safety changes. There is an opportunity to merge technology with clinical care in achieving the goals of this conference. Ultimately, dissemination of the results of this conference will be critical in educating health professionals who will ultimately be responsible for advocating safety changes.

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Use of Sedation Assessment Scales in the ICU: Paying Attention to What We Are Doing

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Key Points

- *Monitoring the level of consciousness of critically ill patients receiving sedative and analgesic medications is important to minimize pain and discomfort and to avoid excessive or unnecessarily prolonged sedation.*
- *A sedation goal should be established that is regularly redefined, and a validated assessment scale used to measure the level of sedation.*
- *Validated sedation assessment scales include the Ramsay Sedation Scale (RSS), Sedation Agitation Scale (SAS), Motor Activity Assessment Scale (MAAS), Vancouver Interactive and Calmness Scale (VICS), Richmond Agitation-Sedation Scale (RASS), Adaptation to Intensive Care Environment (ATICE) scale, and Minnesota Sedation Assessment Tool (MSAT).*
- *The use of sedation scales improves communication among clinicians, reduces the frequency of over-sedation, and aids in implementation of successful sedation management strategies.*

Monitoring the level of consciousness of critically ill patients receiving sedative and analgesic medications is an important component of routine patient care in the intensive care unit (ICU).^{1,2} This is important to satisfy the goals of minimizing pain, discomfort, and intolerance of ICU-related therapy while avoiding excessive or unnecessarily prolonged sedation. There are important differences in clinical characteristics among patients that may influence sedation management and the desired depth of sedation, and the sedation target must be adjusted as the individual patient's condition evolves.

Monitoring the Level of Consciousness: Assessment Scales

Among the various tools available for monitoring the level of consciousness, sedation assessment scales are the most widely used. Expert consensus recommendations include the routine use of a validated sedation assessment tool and establishing a sedation goal that should be regularly redefined.¹ The assessment of sedation and response to therapy should also be systematically documented. In spite of these guidelines, in a recent study of United States aca-

demic medical centers, a sedation scale was used in only 55% of mechanically ventilated patients.

For a sedation assessment scale to be used successfully, clinicians must be confident that it measures what it intends to, is reliable, and is easy to use. Desirable features include

a) development by a multidisciplinary group that is representative of those who use and interpret it, e.g., nurses, physicians, and pharmacists, b) logical structure to the scale such that it adequately covers the full range of responses in a graded fashion, c) rapid to perform and easy to recall and interpret, d) well-defined and mutually exclusive criteria for each level such that there is little likelihood of overlap or confusion, e) sufficient sedation levels to permit medication titration to various end-points as a patient's condition changes, f) an assessment of agitation, and g) rigorous testing of reliability and validity in the patient population for which the scale is intended to be used.³

When one examines the various sedation assessment scales, the domains that are to be evaluated and the structure of the instrument should be considered. The principle

domain of most scales is consciousness, with the range of responses extending from alert to comatose. The most commonly measured sub-domain within the domain of consciousness is arousal or awakeness, often in response to stimuli of increasing intensity. In some instruments higher states of consciousness are further defined by testing cognition or comprehension. A sufficient number of sedation levels are needed in the consciousness domain, so that sedative medications can be titrated more precisely to the desired state of consciousness.

A second important domain is agitation or, conversely, calmness, typically anchored at opposite ends by a calm state and by frankly combative behavior. Whereas agitation is relatively infrequent (5-10%) if a group of patients is examined at a single point in time,⁴ as many as 70% of patients will display agitated behavior at some point during their ICU stay.⁵ Agitation is important to recognize since it may reflect inadequately treated pain, unrecognized delirium, or other problems such as angina or a mal-positioned endotracheal tube. Many conditions and medications can contribute to the development of delirium. Recognition and documentation of agitation may lead to improved management. Some recent sedation assessment instruments broaden the range of assessments to include tolerance of the ICU environment, such as patient-ventilator synchrony.⁶

There are several sedation assessment scales that have been validated in adult ICU populations (Table).

Table. Sedation Assessment Scales Validated in Adult ICU Populations*

Ramsay Sedation Scale (RSS)
Sedation Agitation Scale (SAS)
Motor Activity Assessment Scale (MAAS)
Vancouver Interactive and Calmness Scale (VICS)
Richmond Agitation-Sedation Scale (RASS)
Adaptation to Intensive Care Environment (ATICE)
Minnesota Sedation Assessment Tool (MSAT)

* Listed in order of publication

Although all scales include some measure of arousal or awakeness, there are differences in the domains examined, the construction of the instrument, and the extent of testing of validity and inter-rater reliability.

Ramsay Sedation Scale (RSS)

In 1974, Ramsay and colleagues published the RSS, designed to subjectively grade level of sedation in a clinical trial of sedative agents.⁷ Although not validated nor tested for inter-rater reliability until recently, this scale has been and continues to be widely used. This 6-level scale includes 4 levels of sedation or arousal (levels 3-6), a “cooperative, oriented, and tranquil” level (2), and a single level for an anxious, agitated, or restless state (1). A light-to-moderate level of sedation is depicted by response to spoken word in a single level (3), and deeper levels of sedation are established by examining the response to physical stimulation (a light glabellar tap), ranging from brisk (4), to sluggish (5), to none (6) in a sleeping patient. Inter-rater reliability has recently been shown to be excellent, and RSS correlates well with other sedation scales.^{4,8}

Sedation Agitation Scale (SAS)

In 1994, Riker and co-workers published the SAS that was subsequently modified to its current status in 1999, with an emphasis on expanding the assessment of agitation.^{9,10} This 7 level scale (1-7) includes 3 levels of agitation (5-7), a “calm and cooperative” level (4), and 3 levels of sedation (1-3). In contrast to RSS, the sedation level is established by satisfying one or more measures of arousal and cognition. The SAS has been extensively validated in different patient populations¹⁰⁻¹² and is widely used.

Motor Activity Assessment Scale (MAAS)

The motor activity assessment scale (MAAS), also published in 1999, has structure nearly identical to SAS with 3 levels for agitation (4-6), one level for “calm and cooperative”, and 3 levels for sedation (0-2).¹³ Like SAS, similar criteria are used for the various sedation levels, although the specific criteria differ. The use of several criteria for each level for these scales raises the likelihood that some

patients may satisfy criteria from multiple levels (and not all criteria from any one level), and might impair ease of recall from memory.

Vancouver Interactive and Calmness Scale (VICS)

The structure of the VICS, published in 2000, differs in that separate scores for “interaction” and “calmness” domains are established by summing the caregiver grading of a series of questions.¹⁴ For each domain, there are 5 questions to which the caregiver gives one of 6 responses, varying from “strongly agree” (1 point) to “strongly disagree” (6 points). Patient stimulation is required to address some questions. The scores for the questions are summed with higher scores (maximum 30) corresponding to high interaction and calmness. While demonstrating good reliability and face and construct validity, the complexity of calculation may present a challenge for bedside application.

Richmond Agitation-Sedation Scale (RASS)

In 2002, Sessler and colleagues introduced the RASS, a 10-point scale that addresses both agitation (scores of +1 to +4) and consciousness (scores of -1 to -5) with a “0” score corresponding to a calm and alert state.⁴ Agitation scores range from “anxious” (+1) to frankly combative (+4), based upon observation. Deeper levels of sedation are established using 2 additional steps. First the subject’s response to the tester’s verbal instructions to “open your eyes and look at me” is noted. If the subject opens their eyes (arousal) and follows

the command to look in their eyes (cognition), they receive a score of -1 if the actions are sustained > 10 sec (with prompting) or -2 if < 10 sec. A score of -3 is assigned if there is eye opening, or any other movement to the verbal command, but making eye contact is not performed (arousal without cognition). If there is no response to verbal stimulation, observation of any response to physical stimulation (shoulder shaking followed by sternal rub if no response to shoulder shaking), a score of -4 is assigned, or absence of any movement a score of -5 is assigned. There has been extensive testing of reliability among physician, nurse, and pharmacy caregivers in all adult ICU patient populations, and after implementation in a medical ICU.⁴ Interrater reliability at other institutions and over time has also been established.^{8,15} Extensive evidence of validation, including face and construct validity testing, comparison with other sedation scales, and correlation with processed EEG and limb movement technology has been demonstrated.^{4,8,16}

Adaptation to Intensive Care Environment (ATICE)

The ATICE presents a comprehensive approach with a consciousness domain and a tolerance domain.⁶ There are 5 tests (awakeness and comprehension in the consciousness domain, and calmness, ventilator synchrony, and face relaxation in the tolerance domain), and 20 steps are required to complete testing. There are 6 levels in the awakeness domain, including an alert (eyes opening spontaneously) level. The tests are

performed in a step-wise fashion to address tolerance first, followed by consciousness, and then pain. This strategy has been demonstrated to reduce duration of mechanical ventilation in a longitudinal study design.¹⁷

Minnesota Sedation Assessment Tool (MSAT)

The MSAT contains a 6-level arousal scale which examines eye opening spontaneously or in response to verbal or physical stimuli, and a motor activity scale, a 4-level scale based upon patient movement ranging from no spontaneous movement to movement of the back or abdomen.¹⁸ While the arousal scale was demonstrated to be valid using a number of parameters, the motor scale results were less impressive.

All of these sedation assessment instruments have been demonstrated to be reliable among research personnel, and SAS, RASS, ATICE, and MSAT have been tested for reliability in clinical practice.^{4,15,17-19} These instruments have been tested for face, construct, and /or criterion validity using a broad range of comparators, including visual analogue scales, other sedation scales and instruments, the quantity of sedative drug administered, and expert opinion by caregivers. Some scales (RSS, SAS, RASS) have also been correlated with processed electroencephalography, as well as limb acceleration and movement using actigraphy or digital imaging.^{8,16,20}

Summary

The use of sedation scales improves communication among caregivers, reduces the frequency of over-sedation, and aids in implementation of successful sedation management strategies. The measurement of the level of sedation should be performed in all ICUs, particularly in mechanically ventilated patients, and used as a target for sedative drug titration.

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Assessment and Treatment of Delirium in the ICU

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Key Points

- *Delirium is an independent risk factor for increased length of stay, six-month mortality, intensive care unit (ICU) and hospital costs.*
- *The Confusion Assessment Method for the ICU is a reliable and easy-to-use tool for delirium assessment.*
- *Society of Critical Care Medicine guidelines include recommendations for the treatment of ICU delirium.*
- *To reduce the risk associated with delirium, clinicians should first consider discontinuing or reducing doses of anticholinergics, sedatives and analgesics.*

In 2002 the Society of Critical Care Medicine (SCCM) published a revision of the clinical practice guidelines for the sustained use of sedation and analgesia that included an entire section on the treatment of ICU delirium.¹ The inclusion of this section underscores the importance of monitoring and treatment of patients with delirium to promote optimal comfort for ICU patients. Many healthcare providers think that cognitive impairment is an expected outcome in the ICU patient that is temporary and of little consequence (i.e., part of the “ICU psychosis”). ICU delirium can occur in up to 80% of ICU patients and is an independent risk factor for increased length of stay² and six-month mortality.³ It is therefore vital to consider patient safety in

addition to patient comfort when monitoring and treating delirium.

Definition, Prevalence and Outcomes of Delirium

Many terms have been used to describe delirium including ICU psychosis, ICU syndrome, acute confusional state, septic encephalopathy, and acute brain failure. The Diagnostic and Statistical Manual of Mental Disorders (DSM IV), defines delirium as a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time.⁴ Delirium can be divided into three subtypes according to level of psychomotor activity and alertness: hypoactive, hyperactive, and mixed.⁵⁻⁷

Hypoactive delirium is characterized by lethargic level of consciousness and is often referred to as “quiet” delirium.^{5,6,8} Hyperactive delirium is associated with agitation and characterized by restlessness, fidgeting, pulling out tubes and lines, and sometimes even combativeness.⁵⁻⁷ The mixed subtype is characterized by a fluctuating between hyper and hypoactive.

Delirium is present in up to 80% of ICU patients.⁹⁻¹² Mixed-subtype delirium is the most common (54.9%), followed by hypoactive delirium (43.5%) and purely hyperactive delirium (1.6%).¹³ Despite the high prevalence, delirium is unrecognized in 66% to 84% of patients, whether they are in an ICU, a hospital ward, or an emergency department.¹⁴⁻¹⁶

Delirium is associated with many negative outcomes. Patients with ICU delirium have a three-fold increased risk of death in six months when compared to those without delirium even after controlling for pre-existing comorbidities, severity of illness, coma and the use of sedative and analgesic medicines. Each additional day of delirium was associated with a 20% increased risk of remaining in hospital and a 10% increased risk of

death.³ Delirium is also associated with higher ICU costs (\$22,346 vs. \$13,332) and hospital costs (\$41,836 vs. \$27,106).¹⁷ Delirium may also predispose ICU survivors to prolonged neuropsychological deficits.¹⁸

Assessment

Currently there are two ICU delirium assessment tools: the Intensive Care Delirium Screening Checklist¹⁹ and the Confusion Assessment Method for the ICU (CAM-ICU).¹⁰ The Intensive Care Delirium Screening Checklist is an eight-item checklist with a sensitivity of 99%, specificity of 64%, and inter-rater reliability of 0.94.¹⁹ Each of the eight items is scored as absent or present (1 or 0, respectively) and the item scores are summed for a total score. Patients who score >4 on the total score are considered delirious. The CAM-ICU (Figure), adapted from the Confusion Assessment Method²⁰ for use in non-verbal ICU patients, is a well-validated, widely used delirium assessment scale.⁹⁻¹¹ The CAM-ICU was designed to be a serial assessment tool for nurses and physicians and is easy to use, taking a half minute on average to complete. A recent report from two institutions regarding the feasibility of implementing this new assessment found that even after minimal training nurses were both compliant and accurate with performing the CAM-ICU.²¹ A complete description of the CAM-ICU and training materials can be found on www.ICUdelirium.org.

Prevention and Treatment

Although the exact pathophysiological mechanisms involved in delirium are unknown, imbalances of neurotransmitters such as dopamine, γ -aminobutyric acid, and acetylcholine are thought to be the root cause.^{7,22} Imbalances in these neurotransmitters can result from several factors: reduction in cerebral metabolism, primary intracranial disease, systemic diseases, secondary infection of the brain, exogenous toxic agents, withdrawal from substances of abuse such as alcohol and sedative-hypnotic agents, hypoxemia and metabolic disturbances, and the administration of psychoactive medications such as benzodiazepines and narcotics.

Possible causes of delirium must be considered when formulating treatment plans. For example, neurotransmitter levels are affected by drugs with anticholinergic properties, and psychoactive medications are the leading iatrogenic risk factor for delirium.^{23,24} Benzodiazepines, narcotics, and other psychoactive drugs are associated with a 3- to 11-fold increase in relative risk for the devel-

opment of delirium.²⁵ A recent study found the use of opiates was strongly related to the development of delirium but the use of benzodiazepines and propofol was not.²⁶ In another study, lorazepam was found to be significantly associated with the development of delirium but no significant relationship was found with fentanyl, morphine, or propofol.²⁷ More research is needed to determine the specific medications associated with delirium. When considering treatment options, it is important to consider the various mechanisms that can lead to neurotransmitter imbalances.

Early detection of delirium is important. Treatment efforts should then focus on identifying the cause and removing or reducing the causative factors to improve patients' mental status and reduce safety risks (Table). There are no data regarding primary prevention in the ICU. Outside the critical care area, the following strategies have been shown to decrease delirium: repeatedly reorienting patients, providing cognitively stimulating activities, non-pharmacological sleep protocols,³⁰ early mobilization activities, range-

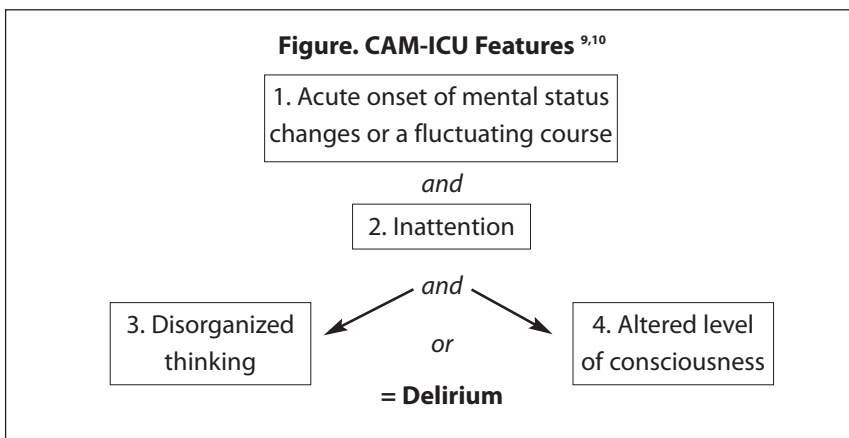


Table. Treatment of Delirium

1. Identify the etiology.
2. Modify risk factors.
3. SCCM Grade C recommendation¹:
Haloperidol (Haldol) 2–10mg IVP q20–30 min,
then 25% of loading dose every 6h (possible side effects:
extrapyramidal symptoms, QT prolongation, torsades de pointes)
4. The atypical antipsychotics (e.g., olanzapine, ziprasidone, and seroquel) may also be helpful in treating delirium, but more research is needed to evaluate these drugs and their effect on this condition.

of-motion exercises, removal of catheters and physical restraints in a timely manner, use of patients' eye glasses and magnifying lenses, use of hearing aids and removing earwax, correcting dehydration, scheduled pain protocols, and minimizing unnecessary noise and stimuli.^{28,29}

When considering pharmacological treatment of delirium, it is essential to first perform a thorough review of the patient's current medications to detect any agents that may be causing or contributing to delirium. This review will reveal any sedatives, analgesics, or anticholinergic drugs that can be discontinued or decreased in dosage.

Although no drugs are approved by the FDA for the treatment of delirium, the SCCM guidelines recommend haloperidol (Table). This Grade C recommendation is based on sparse outcomes data from nonrandomized case series and anecdotal reports.¹ Neither haloperidol nor similar agents (e.g., droperidol and chlorpromazine) have been exten-

sively studied in ICU patients. Patients receiving haloperidol should be monitored for adverse effects such as QT prolongation, arrhythmias, and extrapyramidal effects.¹ Other antipsychotic and neuroleptic agents (e.g., risperidone and olanzapine) may also be helpful for delirium.¹ In fact, a recent study, showed that although both olanzapine (an atypical antipsychotic) and haloperidol were associated with a decrease in delirium, haloperidol was associated with more side effects. Although this was a small, unblinded study lacking a placebo control and the results should be interpreted with caution, it represents the first study to compare the two drugs. Prospective, randomized, controlled trials are needed to evaluate the effectiveness and safety of these agents relative to one another.

Summary

Delirium is a significant problem for critical care patients, affecting 50% of non-ventilated and 80% of ventilated ICU patients. It is associat-

ed with many negative clinical outcomes, including increased mortality. Two valid and reliable tools to monitor for delirium are the Intensive Care Delirium Screening Checklist and the CAM-ICU. Current guidelines recommend the use of haloperidol to treat delirium. It is important to first consider removing or reducing doses of medications that may be contributing factors, such as anticholinergics, sedatives and analgesics. There are many unanswered questions and much room for future study. Given its prevalence and association with negative outcomes, delirium in the ICU cannot be ignored and patients should be actively monitored for this condition. There is a need to find better ways to decrease delirium and thus improve both patient comfort and safety.

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Managing Pain in the ICU Patient

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Key Points

- *Advances in intensive care unit (ICU) technology, specialization, and clinical skills have increased the likelihood of patients surviving critical illness; however ICU patients are still at risk for suffering unrelieved pain.*
- *No valid, reliable physiologic or biochemical measures of pain are currently appropriate for use in the ICU setting, but patient behaviors often can indicate the presence and causes of pain.*
- *Many studies have documented pain associated with common diagnostic and treatment procedures.*
- *Pre-emptive administration of analgesics can be used to help to reduce procedural pain and avoid the development of persistent pain.*
- *Balancing the positive and adverse effects of analgesia and sedation is essential but difficult; daily interruptions of sedative infusions may reduce the incidence of complications, but can result in acute withdrawal syndrome following rapid discontinuation.*

Intensive care units (ICUs) have been developed to provide an environment for the care of critically ill patients. There have been tremendous advances in technology, specialization, and ICU professionals' skills, which have increased the likelihood of ICU patients' surviving their serious illnesses. ICU patients are still at risk for suffering considerable pain from their diseases, injuries, and/or clinical procedures. Several studies have documented the physiological¹ and psychological¹⁻³ costs of ICU patients' unrelieved pain (Table 1).

Pain Assessment

One of the primary causes of inadequate pain management in the ICU is the lack of appropriate pain assessment (Table 2). The use of well validated pain assessment instruments^{4,5,7} can be difficult in ICU patients. Professional practice standards and regulatory mandates⁸ require that pain assessments be attempted for all patients. No valid or reliable physiologic or biochemical measures of pain are currently appropriate for use in the ICU setting, but pain-associated behaviors often indicate the presence and causes of pain.

Table 1. Challenges of Unrelieved Pain

Physical suffering

- 40% of 80 post-ICU ARDS patients recalled having pain while in ICU
- 40% higher frequency of chronic pain than in controls¹
- 87% of 97 post-ventilation patients remembered being moderately to extremely bothered by pain²

Psychic suffering

- Significantly higher PTSD scores in post-ICU ARDS patients than in controls (28% vs. 12%)¹
- Traumatic memories associated with pain after cardiac surgery (81.6% of 184 patients)³

Puntillo and colleagues⁹ noted a significant relationship between behavioral indicators of pain observed by nurses and the nurses' ratings of postoperative patients' pain intensity. Payen and colleagues¹⁰ reported validation of a pain behavior scale (PBS) in a sample of 30 intubated, sedated ICU patients. Using a model in which patients underwent common noxious and non-noxious procedures, they found that the percent of patients exhibiting no pain behaviors was significantly lower in the patient group that underwent a non-noxious procedure than in the group that underwent a noxious procedure. More recently a behavior observation scale was developed and tested in a large sample of patients undergoing common procedures such as wound care, wound drain removal, and turning.¹¹ By comparing behaviors exhibited before and during the procedure, and behaviors in patients with and without procedural pain (as noted on a 0-10 numeric rating scale), the researchers identified specific procedural pain behaviors that included grimacing, rigidity, wincing, shutting of eyes, verbalization, moaning, and clenching of fists. Patients with procedural pain were 2.8 times more likely to have increased facial responses, 4.1 times more likely to have increased body movement responses, and 10.3 times more likely to have increased verbal responses during the procedure than patients without procedural pain. Despite these studies, there is still a need for a valid, reliable, and feasible behavioral assessment methods for ICU patients.¹²

Pain Management

Pain assessment is an essential step before pain intervention, but pain intervention can be provided even before a pain stimulus. Preemptive analgesia is the administration of an analgesic agent before the patient experiences a noxious stimulus to prevent amplification and hyperexcitability of the central nervous system (CNS). Hyperexcitability may lead to CNS sensitization, which can result in persistent pain. Patients may not receive preemptive analgesia before procedures because health professionals are unaware of the degree of pain associated with various common procedures. Many studies have documented the pain associated with procedures such as arterial blood gas draws, nasogastric tube insertion, intravenous (IV) catheter insertion, mechanical ventilation,¹³ turning, wound drain removal, wound care, tracheal suctioning,^{14,15} and chest tube removal.^{14,16,17} Planning for these procedures should include consideration of the optimal preemptive analgesic intervention. Analgesic administration should be timed so that the selected drug's peak effect is

obtained at the time of the procedure. Puntillo and Ley¹⁸ demonstrated that pain associated with chest tube removal was minimal when patients were given either IV ketorolac or IV morphine before the procedure at a time that will achieve a drug's peak effect during the procedure.

Opioid and Sedative Therapies

Opioid analgesic therapy remains the primary pharmacologic treatment modality for ICU patients. Based on a review of the most recent evidence, Jacobi and colleagues⁴ have developed clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill. Organ dysfunction and hemodynamic abnormalities in critically ill patients can result in significant inter-individual variability in the pharmacokinetics and pharmacodynamics of drugs. For a given patient, a standard drug dose could be toxic, subtherapeutic, or effective.

It is not unusual for critically ill patients to receive a combination of opioid and sedative therapies, so proper use of multiple, potentially interacting medicines can be chal-

Table 2. Pain Assessment in Patients Who Cannot Self-report

- No valid or reliable physiological or biochemical measure of pain
- Pain behaviors have been validated in acutely/critically ill patients undergoing procedures
- Behavioral Pain Scale validated in critically ill, sedated patients¹⁰

Table 3. Balancing Analgesia and Sedation is Essential but Elusive

- Combination of analgesics and sedatives common in ICU
- Challenges:
 - Tools that differentiate pain from anxiety/agitation exist, with limitations^{14,15}
 - Choosing right type and combination of medications
 - Need new ways to assess pain and discomfort in all ICU patients

lenging (Table 3). One or both types of agents may adversely affect the patient's hemodynamic or respiratory status. The use of both treatments may have synergetic adverse effects. The clinical challenge is to use the right type and combination of medications while avoiding adverse effects. Another challenge is to use tools that differentiate among pain, anxiety, and agitation, so that pharmacological interventions can be targeted to more clearly defined goals. Without the use of such tools, patients may be under-, over-, or "mis"-dosed.

Daily interruptions of sedative infusions for the purpose of assessing the patient have become standard practice in many ICUs. Kress and colleagues¹⁹ showed that in ICU patients daily interruptions of sedative infusions reduced the incidence of many complications and did not result in negative psychological outcomes.²⁰ Interruptions in sedative infusions should include pain and agitation assessments, and be minimized in

patients who respond adversely to them. In patients who have been receiving opioids and benzodiazepines for more than a few days, interruptions can result in a withdrawal syndrome. Cammerano and colleagues²¹ showed that ICU patients who received analgesic and sedative medications for longer than seven days experienced acute withdrawal syndrome after rapid discontinuation of medication.

Summary

Although advances have been made in pain assessment and treatment for patients in the ICU, gaps remain. There are no comparative trials of opioids,⁴ and the evidence for most recommendations made by the most current guideline panel⁴ is based on observational studies rather than randomized clinical trials. Until more evidence-based practice tools and guidelines become available, clinicians will need to use available practice-based assessment tools to promote patient comfort and safety.

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The Role of Brain Monitoring in the ICU

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Key Points

- *Mental well-being is as important than physical well-being.*
- *Brain monitoring can detect, prevent and provide a prognosis for cerebral insults.*
- *Cerebral function monitoring is a patient safety strategy.*

Monitoring mental well-being is as important as monitoring the performance of other major organ functions. Cerebral function, however, is not always monitored in the critical care or perioperative setting. Monitoring brain function effectively and reliably is the next major challenge of intensivists and anesthesiologists.

Cerebral cortical function may be affected by cerebral perfusion, hypoxia, pharmacological agents, seizure activity, cerebral metabolism, and neuronal dysfunction. Instruments for monitoring brain function include subjective measures, such as the assessment of depth of sedation or severity of delirium by scoring systems, and objective measures that assess cerebral cortical activity, responses to evoked potentials, cerebral oximetry, and transcranial Doppler ultrasound. The success

of these monitors in providing consistently accurate information about the cerebral state is dependent on many factors: the suitability of the target area of the brain monitored to accurately reflect cerebral state, and the medications and combinations of medications administered. It also depends on the algorithms developed to present the information monitored in a clinically useful form, and the suppression of extraneous noise and other confounding factors. Many studies have analyzed the effectiveness of using cerebral function monitors not only to guide depth of sedation, but also to prevent unintended awareness in the paralyzed patient. The real value of these monitors may well be in improving patient safety by detecting cerebral insults early, allowing appropriate intervention to be made, and predicting outcome.

The use of a multimodal approach to cerebral monitoring may provide a more comprehensive approach to detecting potential cerebral compromise and monitoring the effects of corrective actions.

Consciousness

The conscious state is difficult to define; we know it when we see it but we would probably all have a different definition. It is a biological phenomenon and consists of qualitative subjective states of perceiving, feeling, thinking, information processing and awareness. Where in the brain does consciousness exist? Is it a cortical function or does it arise from deeper areas in the brain and is related to corticothalamic-thalamocortical reverberations? Everyday consciousness is altered by natural sleep, medications such as sedatives and anesthetics, and the effects of self-indulgence. Does how deeply unconscious a person becomes affect how well they recover? A growing body of outcome data suggest that deep sedation and anesthesia may be associated with sequelae such as cognitive deficit and, in an older patient, increased mortality at one year.

Monitoring brain function is a vital component for managing the well-being of the patient undergoing anesthesia and sedation therapy. With most sedation and anesthetic agents, the transition from light sedation to deep sedation and then through general anesthesia to “burst suppression” or coma may occur very rapidly. Whether this is a linear progression or is a series of definite steps in the transition from consciousness to unconsciousness is the focus of significant research.

In 1937 Guedel described four stages of anesthesia in patients undergoing open ether induction. Ninety years earlier Snow had described five degrees of narcotism that followed his close observation of mental state, respiratory pattern and pulse characteristics. Johns recently described a cascade of six neuro-physiologic steps that occurred during induction and recovery from anesthesia. The concept that depth of anesthesia and sedation can be measured on a linear 0-100 scale derived from the cortical activity of the brain may not reflect the actual process. The development of sensors that can probe the deeper levels of the brain may be necessary before the state of consciousness can be accurately monitored.

Sedation Monitoring

The consequences of poorly managed sedation have long been known, yet tight control of sedation is still not universal in critical care units. Virtually every patient admitted into the intensive care unit (ICU) is administered sedation therapy. The precise control of the depth of seda-

tion is often not well managed. Patients often are over- or under-sedated with an accompanying increase in morbidity, mortality and cost. The effective management of pain, anxiety and sleep (hypnosis), together with maintenance of an optimal level of comfort and safety, are the major aims of a sedation therapy regimen. Patient-specific care is evolving to the point where titratable, target-specific medications can be administered that reduce side effects, modulate the stress and inflammatory responses and reduce ICU stay. Effective pain management with minimal side effects is the foundation of a well-controlled sedation program.

In 1974, the concept of controlling sedation in the ICU and the first sedation scoring system, the Ramsay Sedation Scale,¹ were developed. The same level of intense management provided for all other organ systems was proposed for brain function. Studies have since shown that optimizing sedation management improves patient outcomes, shortens ICU length of stay, and significantly reduces costs.

Both subjective and objective tools are available to aid in the assessment, re-assessment, and adjustment of therapy, to help avoid over- or under-sedation and their consequences, and to manage these patients more precisely. Sedation scales are subjective tools for bedside evaluation of patients, while brain cortical activity monitors provide objective monitoring of the response to sedation therapy and help achieve an optimum level of

consciousness.

Critical care physicians must continually reassess and redefine the sedation strategy for their patients as the clinical state changes. Having protocols for administering sedation, analgesic, anxiolytic, antidelirium and paralytic medications, and sedation monitoring tools, is important.

Drugs used for sedation include analgesics, sedatives, and neuroleptics. All of these agents have adverse consequences associated with their use, such as respiratory depression, abuse potential, lack of orientation and cooperation, delirium, hypotension, and tolerance. Other effects include hyperlipidemia with propofol, constipation with opioids, and delirium with the benzodiazepines. A new agent in ICU sedation is dexmedetomidine, an alpha-2 adrenoagonist that acts on the locus ceruleus/norepinephrine axis rather than on the GABA receptor, and provides non-REM sleep, sedation, and anxiolysis without respiratory depression and with an opioid-sparing capacity. This drug offers a more innovative approach to controlled, co-operative, comfortable sedation.

Protocols should be developed that enable a patient to be comfortable, pain free, and safe, and shorten the ICU length of stay. Poor control of sedation is no longer acceptable as a standard of care in the ICU.

Brain Function Monitors

The measurement of brain cortical electrical activity was first described in humans by Hans Berger in 1929. Within 10 years the effect of anesthetic agents on the electroen-

cephalogram (EEG) was noted, but the clinical utility of this instrument for monitoring depth of sedation and cerebral well being during surgical procedures was not developed until 1969. Maynard constructed a two-channel cerebral function monitor that could record cerebral electrical activity as a continuous power strip. Investigators were able to use this device to evaluate cognitive outcome after cerebral insult during cardiopulmonary bypass procedures. The utility of the cerebral function monitor as a diagnostic and predictive clinical tool was developed.

The EEG opens a window on the cortical brain electrical activity, which is a sensitive marker of brain ischemia and hypoxia. The EEG may also indicate the depth of pharmacological sedation by recording the transition to low-frequency, high-voltage activity. One of the limitations of EEG monitors is that they use a frontal array only and this change is

heterogeneous across the cerebral cortex.

It is important to be able to assess the depth of sedation in the ICU patient as objectively as possible to consistently attain the desired level. There are two types of monitors that examine electrical activity: those that assess cortical activity as a raw signal, a power spectral array or an entropy analysis; and those that assess the responsiveness of the brain to evoked potentials. The most commonly used brain monitors that use the latter technology are the Bispectral Index (Aspect Medical System, Newton, MA), the Patient State Index (Hospira, Lake Forest, IL), Auditory Evoked Potentials (CareFusion San Diego, CA) and Entropy (GE HealthCare, Fairfield, CT). Other companies with similar technologies are developing new products of the same type.

Another approach to monitoring cerebral well-being is the cerebral

oximeter (Somanetics Corp. Troy, MI). This device uses dual-wavelength, near-infrared spectroscopy to measure regional cerebral oxygen saturation. It is ideally suited to indicate change in the balance of oxygen supply and demand. Low oxygen saturation found intraoperatively in cardiac surgery patients is associated with increased time on mechanical ventilation, time in ICU and length of stay in the hospital postoperatively.

Summary

Technology that improves the assessment of cerebral well-being is getting better. As regular use of brain function monitors increases, this will stimulate the development of this technology to the degree of sophistication that we have reached with cardiac monitoring. It is incumbent on all of us to continually evaluate the art and science of brain function monitoring and consider where it fits in our practices.

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PROCEEDINGS

Clinical Pharmacology of Sedatives in the Critically Ill

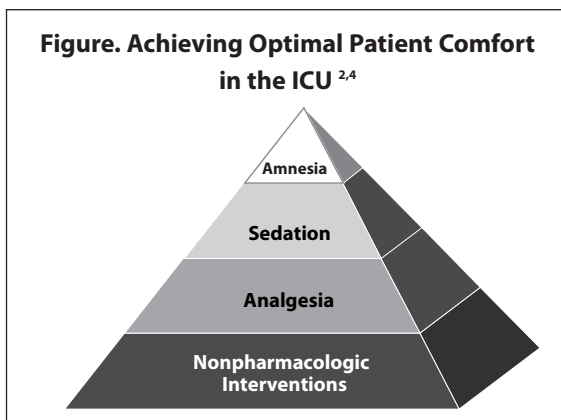
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Key Points

- Sedatives are often used in critically ill patients to manage anxiety, agitation, and delirium.
- No agent being used clinically today has all the characteristics of an ideal sedative.
- Some of the characteristics of an ideal sedative are shared by the sedatives used most commonly, such as benzodiazepines, propofol, dexmedetomidine, and haloperidol.
- These four sedatives differ with regard to mechanism of action, clinical pharmacology, pharmacokinetics, pharmacodynamics, and comparative side effect profiles.

Anxiety, agitation, and pain are problems frequently encountered in critically ill patients. Increasingly, delirium also has been recognized as a significant complication of critical illness.¹ Consensus guidelines were published by the Society of Critical Care Medicine in 1995 and revised in 2002 in an attempt to optimize management of these problems.^{2,3} Non-pharmacologic strategies and analgesics form the foundation of these guidelines (see Figure).^{2,4} In most instances, however, additional sedative therapy is needed in combination with anal-

gesics to provide comfort and facilitate care of the critically ill patient. Characteristics of the ideal sedative in this setting have been outlined previously (see Table 1).⁵ Unfortunately, no sedative is currently available that possesses all of these attributes. Nevertheless, considera-



tion of these characteristics provides an excellent framework in which to compare the clinical pharmacology of those agents routinely used in managing anxiety, agitation, and delirium in the critically ill. The sedatives that will be outlined in this article include the benzodiazepines, propofol, haloperidol, and dexmedetomidine.

Table 1. Characteristics of the Ideal Sedative in Critically Ill Patients.^{4,15}

- Rapid onset of action
- Rapid recovery after discontinuation
- No active metabolites
- Easy to titrate to desired level of sedation
- Easy to administer
- Few adverse effects
- Lack of tolerance
- Lack of withdrawal symptoms
- Minimum drug interactions.
- Metabolism and/or elimination not dependent on hepatic or renal function
- Inexpensive

Benzodiazepines

Mechanism of Action and Pharmacologic Effects

The effects of benzodiazepines are mediated through binding to a specific site on the γ -aminobutyric acid (GABA) receptor.⁶ Stimulation of the benzodiazepine-GABA receptor complex produces general inhibition of neuronal impulses and blocks the encoding of new information and unpleasant experiences within the limbic system.^{2,6} The effect is a concentration-dependent anxiolysis and anterograde amnesia at lower doses and sedation-hypnosis at higher doses.⁷ The benzodiazepines also possess muscle relaxant and anticonvulsant pharmacologic properties that are useful in selected critically ill patients.

Pharmacokinetics/ Pharmacodynamics

The three benzodiazepines used clinically for sedation in the critically ill patient are diazepam, midazolam, and lorazepam. The pharmacokinetic properties of these three drugs are outlined in Table 2. Variable effects between these agents such as onset of action and duration of action can be readily explained by differences in their physiochemical properties. For example, diazepam is highly lipophilic,

resulting in rapid distribution into the brain as well a relatively short duration of action upon redistribution into peripheral tissues. In contrast, lorazepam is the least lipophilic of the three benzodiazepines in clinical use. Thus, it crosses the blood-brain barrier more slowly compared with diazepam and midazolam, which results in a delayed onset of action yet produces a much longer duration of action.

Another major distinguishing characteristic between the agents is the formation of active metabolites for diazepam and midazolam, while lorazepam does not have any active metabolites. The presence of active metabolites can dramatically affect the pharmacodynamic effects of long-term dosing of diazepam and midazolam, compared with single-dose effects. For example, while midazolam has a predictable pharmacokinetic profile when given as a bolus dose or short-term infusion, prolonged over-sedation has been

observed in patients receiving long-term infusions or those with hepatic dysfunction.^{8,9} Furthermore, since the active metabolites for diazepam and midazolam are eliminated by the kidneys, the potential for accumulation of the metabolite and prolongation of effect should be considered in critically ill patients with renal insufficiency. Protein-binding alterations can also alter the effect of these agents, since all are relatively highly protein bound.

Side-Effect Profile

The benzodiazepines as a class are a relatively safe group of drugs.⁶ However, the potential for respiratory depression and hypotension does exist, especially when used in combination with opiate analgesics. Acute and chronic tolerance has been described with benzodiazepines use, as well as paradoxical responses.¹⁰ This latter phenomenon is particularly common in elderly patients.

Diazepam is metabolized by the

Table 2. Pharmacokinetics of Sedatives Used Routinely in Critically Ill Patients^{2,7,11}

Drug	Onset of Action (minutes)	Half-life (hours)	Protein Binding (%)	Metabolism	Active Metabolites	Route of Elimination
Diazepam	2-5	20-120	99	Hepatic oxidation	Yes	Parent: liver Active metabolite: renal
Lorazepam	5-20	8-15	91	Hepatic conjugation	None	Parent: liver
Midazolam	2-5	3-11	95	Hepatic oxidation	Yes	Parent: liver Active metabolite: renal
Propofol	1-2	26-32	98	Hepatic conjugation	None	Liver
Dexmedetomidine	5-10	2-7.5	94	Hepatic oxidation	None	Liver
Haloperidol	3-20	18-54	92	Hepatic oxidation	Yes	Liver

cytochrome P450 CYP2C19 subfamily in the liver.⁶ The potential for genetic polymorphisms and interactions with other drugs metabolized by this pathway (e.g., amiodarone, fluconazole, omeprazole, valproic acid) can make the response to diazepam more unpredictable compared with alternative sedatives.⁶ Similarly, midazolam is metabolized by the CYP3A4 enzyme subfamily. As such, the potential for drug interactions with inhibitors of this isoenzyme, such as macrolide antibiotics, diltiazem, cimetidine, propofol, verapamil, and fluconazole, can result in accumulation of the parent compound.⁶

Lorazepam is formulated in polyethylene glycol and propylene glycol.⁶ While small, usual dosages of lorazepam result in inconsequential amounts of these excipients being administered, long-term infusions and higher-than-normal dosages have been associated with lactic acidosis, hyperosmolar coma, and nephrotoxicity.^{2,7} Precipitation of lorazepam can also occur if not diluted according to the manufacturer's recommendation.⁷

Propofol

Mechanism of Action and Pharmacologic Effects

Propofol's pharmacologic effects are not entirely known, although are likely mediated through activation of the GABA_A receptor at a site distinct from the benzodiazepines.¹¹ Clinically, propofol produces anxiolysis and hypnosis, as well as having beneficial effects on intracranial pressure in patients with traumatic brain

injury.¹² It has essentially no analgesic properties and less amnestic effect than the benzodiazepines.^{5,11}

Pharmacokinetics/ Pharmacodynamics

As a consequence of its high lipophilicity, propofol has a very rapid onset of action and a short duration of action. While an attractive option when rapid awakening is desired, the wake-up time may be significantly prolonged in patients receiving infusions for several days or longer. Since the effect of propofol is largely affected by its distribution into fatty tissue, its elimination is minimally affected by hepatic or liver dysfunction, which is an attractive feature in critically ill patients with co-morbidities.

Side-Effect Profile

Hypotension is one of the major side effects associated with propofol use. Respiratory depression also can be observed when combined with the benzodiazepines or opiates.^{5,7} Propofol is water insoluble and formulated as an oil-in-water emulsion that provides 1.1 kcal/mL from fat.⁵ As such, hypertriglyceridemia is a potential effect in critically ill patients receiving relatively high doses of propofol. In patients receiving propofol the additional caloric intake should also be considered as part of the overall nutritional supplementation to avoid excessive caloric intake.² Other potential problems related to its lipid formulation include infectious complications and drug incompatibilities.⁵

A potentially life-threatening complication associated with excessively high doses of propofol is known as the "Propofol Infusion Syndrome."¹³ This syndrome is characterized by metabolic acidosis, bradycardia, hepatomegaly, hyperlipidemia, dysthythmias, rhabdomyolysis and cardiac arrest.¹³ While originally reported in pediatric patients, it has subsequently been reported in adults as well.¹³

Dexmedetomidine

Mechanism of Action and Pharmacologic Effects

Dexmedetomidine is a potent α_2 -adrenoreceptor agonist that possesses similar pharmacologic properties to the prototypical antihypertensive drug from this class of drugs, namely, clonidine. Activation of the postsynaptic α_2 -adrenoreceptor in the central nervous system results in inhibition of norepinephrine release presynaptically and sympatholysis.⁷ The resulting pharmacologic effects observed with dexmedetomidine are sedation and analgesia.

Pharmacokinetics/ Pharmacodynamics

Dexmedetomidine is rapidly distributed upon administration with a half-life of approximately 2 hours.¹⁴ Based on its linear kinetic profile, dose titration to the desired sedative effect is relatively straightforward.^{7,14} While dosage reductions are warranted in patients with hepatic dysfunction, no dosage adjustment is needed in patients with renal insufficiency.

Side-Effect Profile

Hypotension and bradycardia resulting from the sympatholytic effects of dexmedetomidine are two of the more significant side effects associated with the use of this sedative in the critically ill patient. One major advantage of dexmedetomidine is the relative lack of respiratory depression with its use. The ability to easily arouse patients receiving dexmedetomidine from a sedated state ("cooperative sedation") is also deemed to be a distinct advantage in selected critically ill patients.^{7,14}

Haloperidol

Mechanism of Action and Pharmacologic Effects

Haloperidol is a butyrophenone neuroleptic that antagonizes dopamine-mediated neurotransmission in the basal ganglia of the brain. Pharmacologically, haloperidol has the effect of reversing or diminishing hallucinations, delusions or unstructured thought patterns. Thus, haloperidol has utility in treating delirium in the critically ill patient.

Pharmacokinetics/

Pharmacodynamics

Haloperidol's onset of action occurs within minutes although its duration of activity is relatively long.

Dosing often requires repeated intravenous injections until the desired outcome is observed.

Side-Effect Profile

Haloperidol can produce serious dysrhythmias (e.g., QTc prolongation, torsade de pointes) especially with large daily doses. Extrapyramidal side effects have also been associated with its use. Hypotension can also occur due to α -adrenergic blocker properties. A rare condition known as the neuroleptic malignant syndrome can develop in patients receiving haloperidol.

Summary

Use of sedatives in the critically ill is an important yet highly challenging task for clinicians. The agents most commonly employed for treatment of anxiety and agitation, and minimization of stress in the intensive care setting are the benzodiazepines, propofol, and more recently, dexmedetomidine. Haloperidol is the drug of choice for the treatment of delirium. A firm understanding of the clinical pharmacology of these agents is imperative for their optimal use in the critical care setting.

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PROCEEDINGS

SCCM Guidelines for Sedation Management: Development and Use in Clinical Practice

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Key Points

- Guidelines for the sustained use of sedatives and analgesics have been proposed to improve efficacy and safety.
- Improved use of sedation has the potential to reduce the duration of mechanical ventilation, intensive care unit length of stay, the use of neuromuscular-blocking agents, and the cost of sedative agents.
- Sedation complications may be specific to the agent utilized (e.g., propofol, lorazepam, and remifentanyl).
- Reports vary on the clinical and cost improvement resulting from sedation guidelines implementation.
- To realize the potential benefits of sedation guidelines implementation, clinicians will need to measure the impact of these interventions, and re-evaluate and re-educate as needed to maintain adherence with them.

Guidelines for the treatment of a variety of conditions have been proposed to maximize the effectiveness of patient care, while minimizing the risks. The development and implementation of clinical practice guidelines require a multi-professional, team effort. Education and ongoing reinforcement or intervention may be needed for sustained adherence to these guidelines. Improved use of sedation medications has the potential to reduce the duration of mechanical ventilation, intensive care unit (ICU) length of stay, the use of neuromuscular-blocking agents (NMBAs), and the cost of sedative agents.

Guidelines for the sustained use of sedatives and analgesics were published in 2002 by the Society of Critical Care Medicine (SCCM) and the American Society of Health-Systems Pharmacists (ASHP).¹ Important components of the sedation guidelines included a focus on optimal analgesia with systematic assessment of agitation and sedation using a validated scale. The guidelines recommend the use of intermittent anxiolysis in conjunction with analgesia as the recommended starting point, while recognizing that some patients may benefit from continuous-infusion sedation (need for

ongoing or deep sedation). The risks of continuous sedation include excessive sedation and prolongation of mechanical ventilation or complications such as ventilator-associated pneumonia. Deep levels of sedation and amnesia have also been associated with delirium, hallucinations and post-traumatic stress disorder.^{2,3} Sedation complications may be specific to the agent utilized.

Propofol

Propofol-related infusion syndrome is a potentially life-threatening complication associated with high doses of propofol. The syndrome features cardiac failure, rhabdomyolysis, lactic acidosis, and renal failure, but has not been systematically defined. Vasile and colleagues have summarized the published cases and proposed a mechanism for a propofol-related infusion syndrome (PRIS).⁴ While they detail only 14 cases of PRIS in adults, they commonly were fatal. The use of high-dose propofol or prolonged therapy, perhaps in conjunction with catecholamines and steroids, may be triggering factors that lead to PRIS, although a primary or secondary defect in mitochondrial metabolism altering the respiratory-chain complex or fatty-acid oxidation may also

be a factor.⁵ Thus, propofol remains a preferred agent for limited dosing in short-term sedation. Patients receiving high dose or long-term propofol infusions should have triglyceride concentrations monitored and be screened for lactic acidosis.¹

Lorazepam

Lorazepam is the recommend agent for long-term sedation.¹ Metabolism via glucuronidation and the lack of active metabolites are desirable characteristics. Lorazepam and midazolam pharmacokinetics and dynamics were compared in 24 elderly post-operative males receiving target-controlled infusions with a goal concentration of 50 ng/mL.⁶ The infusions were titrated to a modified Ramsay scale without the use of intravenous bolus doses. At the same target level of sedation, lorazepam serum concentrations were approximately half of the midazolam con-

centrations; however, the amnestic effects were approximately 4:1 for lorazepam to midazolam (Figure 1). The pharmacodynamic effects assessed were time to awakening and time to extubation.⁶ Midazolam patients awakened after 3 ± 2.6 hours versus 8.7 ± 5.9 hours for lorazepam. Times to extubation were 5.4 ± 2.4 hours versus 21.2 ± 15.9 hours for midazolam vs. lorazepam, respectively. The longer awakening time for lorazepam may have been the result of context-sensitive half-times from a longer infusion: 36.9 ± 31 hours for lorazepam versus 15 ± 3 hours for midazolam. The potential impact of midazolam metabolite accumulation was not assessed due to the short duration of the clinical trial.

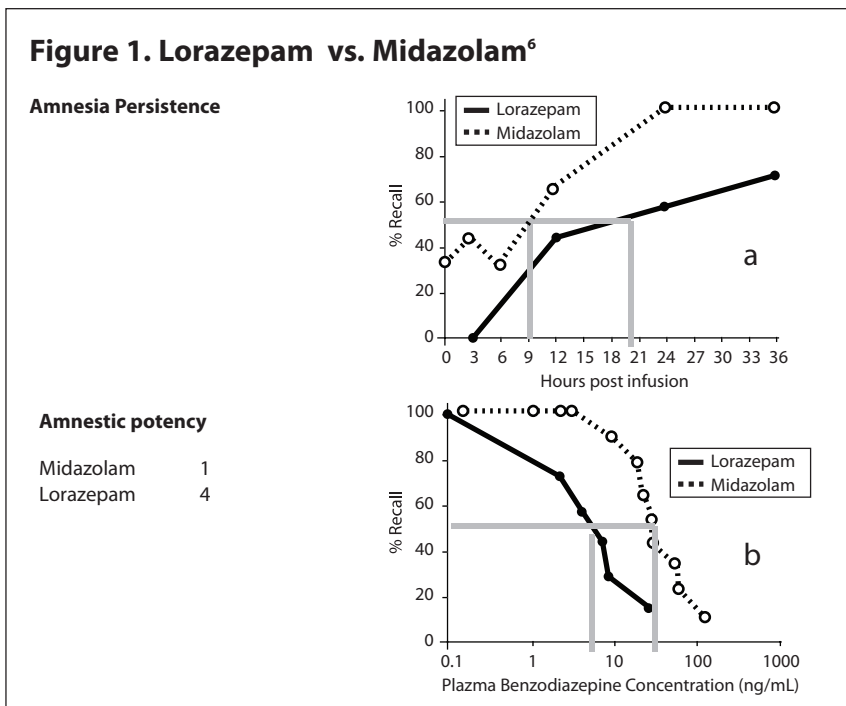
In addition to oversedation, another reason to limit lorazepam doses relates to the propylene glycol (PG) solvent. Two reports have shown

a linear relationship between PG concentrations and osmol gap.^{7,8} The lower-level PG concentration and corresponding osmol gap that pose a risk for renal failure or acidosis are unknown, but lorazepam doses above 10 mg/hr produced a very high PG concentration and osmol gap above 20 (Figure 2).^{7,8}

Remifentanil

The use of short-acting agents to maximize analgesia with sedation has received further study. Remifentanil is an ultra-short-acting opioid-receptor agonist that is metabolized by blood and tissue esterases with an elimination half-life of less than 10 minutes. It may be a particularly useful agent for neurosurgical patients requiring periodic awakening for neurologic assessment. Two recent clinical trials have documented a potential role of remifentanil in the ICU. Muellejans and colleagues compared remifentanil and fentanyl for analgesia of 196 cardiac ICU patients requiring up to 24 hours of sedation.⁹ Propofol infusion was added if opioid administration exceeded a pre-defined dose. This study demonstrated similar efficacy for the two opioids titrated to a standard sedation scale, but more pain in the remifentanil group post-discontinuation.

Remifentanil was also compared with morphine in 40 surgical ICU patients.¹⁰ Remifentanil produced optimal sedation for a greater percentage of time with less frequent dosing changes. The mean duration of mechanical ventilation (14 vs 18 hours), extubation time (17 vs. 73



minutes) and ICU discharge time (20 vs 42 hours) were significantly lower in the remifentanyl group compared with the morphine group, respectively. Midazolam was available for supplemental sedation when the opioid dose exceeded a pre-defined dose. Midazolam was needed by more of the patients treated with morphine than remifentanyl. Remifentanyl does appear to have some advantages over other sedating/analgesic agents, although the risk of tolerance with ongoing infusion remains to be fully defined. Remifentanyl has a higher acquisition cost than other opioids, although drugs constitute a relatively insignificant component of the \$1500 cost per day of mechanical ventilation.¹¹

Impact of Sedation Guidelines Implementation

Bratebrø and colleagues implemented a sedation protocol in 1999 in a ten-bed surgical ICU.¹² The level of sedation was defined twice daily and intervention to maintain the target sedation score (based on the Motor Activity Assessment Scale) reduced ventilator time by 2 days and mean

length of stay by 1 day. Mascia and colleagues also implemented a protocol for the use of sedatives, analgesics, and NMBAs.¹³ They demonstrated a significant reduction in NMBA use and sedation drug costs, despite a higher severity of illness in the guideline population.

Unfortunately, not every report has shown this same benefit following sedation guideline implementation. MacLaren and colleagues implemented a sedation protocol in a 24-bed medical/surgical ICU.¹⁴ The protocol patients (n=86) had greater use of NMBA, longer time on mechanical ventilation, and a longer time to extubation, but lower drug expenditure per hour and improved sedation quality with a greater percentage of time at the Ramsay sedation goal compared with historical controls having a similar severity of illness. The impact of this protocol was greatest on patients requiring long-term sedation.

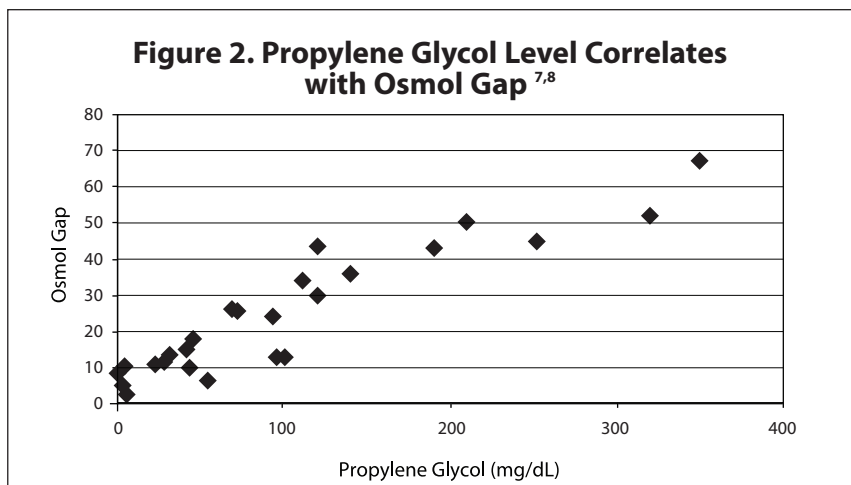
Further examination of sedation costs were reported in a three-month audit of 155 general ICU patients.¹⁵ A sedation protocol was used and the

most common agents were propofol (88%), alfentanil (68%), morphine (30%), and midazolam (25%). Half of the patients had an ICU length of stay greater than two days, and these patients accounted for 94% of the drug expenditure.

Long-term patients in the ICU are the optimal targets for cost-reduction strategies, especially those on mechanical ventilation. The sedatives themselves constitute less than 1% of the total daily cost of ICU care. However, inappropriate use of sedatives can contribute to ICU costs by delaying liberation from mechanical ventilation. Dasta and colleagues evaluated hospital billing data from 253 US hospitals.¹¹ Daily costs were calculated from hospital-specific charge-to-cost ratios. The mean incremental daily cost of mechanical ventilation also was calculated. Costs were greatest in the first three days, but then stabilized such that costs for patients on mechanical ventilation were an average of \$1522 higher per additional day of ventilation. While a formal evaluation has not been performed, these data suggest that a short-acting sedative may have an economic advantage over agents that contribute to delayed awakening and extubation.

Summary

A growing body of literature challenges clinicians to incorporate practice guidelines into daily patient care. In order to achieve potential benefits such as reduction in duration of mechanical ventilation, ICU length of stay, the use of NMBAs and cost of sedative agents, clinicians will



need to measure the impact of these interventions, re-evaluating and re-educating as needed to maintain adherence.

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PROCEEDINGS

Nursing Issues Related to Sedation Management

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Key Points

- *Sedation for the treatment of agitation has become an important issue because critically ill patients are being maintained for long periods of time on complex life support systems.*
- *Successful management of sedation involves complex nursing issues that need to be recognized and addressed to provide effective treatment of agitation and ensure patient comfort and safety.*
- *Patient-related factors that need to be considered for sedation include the complexity of concomitant disease states, rapidly changing hemodynamic status, and altered pharmacokinetics.*
- *Challenges in sedation management include differentiating agitation from other conditions such as pain, standardizing the assessment of agitation, and obtaining multidisciplinary agreement about treatment interventions and priorities.*
- *In addition to bedside decision-making issues, other factors include staff attitudes and perceptions of comfort, family member's perception of agitation, nurses' workload, staffing ratios, and nurses' experience and ability to multi-task amidst rapidly changing conditions.*
- *New approaches to nursing education and evolving technologies have the potential to offset increased bedside practitioner workload, improve communication, and help address the nursing issues related to the sedation management.*

Sedation of critically ill patients has become an important issue because patients can be maintained for long periods of time on complex life support systems. These systems are often uncomfortable, frequently painful, and may require almost com-

plete patient immobility. Anxiety and agitation are common in the intensive care unit (ICU). Despite the frequency of these conditions in the acutely ill patient, the bedside implementation of a multidisciplinary treatment plan to address them

remains challenging. There are complex nursing issues related to managing sedation that need to be recognized and addressed to provide effective treatment of agitation and ensure patient comfort and safety. These issues include patient-specific variables, factors affecting bedside staff, and interfering forces.

Patient-related Factors

Agitation is a continuum of continuously changing physiologic states with varying patient behaviors and responses that depend on the severity and complexity of their conditions. ICU patients typically have complex disease states with rapidly changing hemodynamic status, so that their agitation and requirements for treatment fluctuate over time. A patient's underlying condition and unpredictable hemodynamic status often trigger multi-system organ derangements that alter the pharmacokinetics of medications that are administered. A single dose of medication may be administered, when suddenly the patient's blood pressure falls, the ventilator starts to alarm, and the nurse has to immediately decide which syringe to grab, which pump to grab, which monitor to assess first, and perhaps other

responses – and document everything. Constantly changing variables mean that bedside clinicians need to reassess and redefine the goals of therapy frequently.

ICU patients often have multiple organ derangements. For example, a general care unit patient may have had some degree of respiratory failure, been intubated, and be transferred to the ICU. Upon arrival in the ICU, this patient may have no blood pressure, no intravenous (IV) access, and need four to five medications, all of which should be administered simultaneously. Two or three patients may arrive in the ICU with similar problems. Many ICUs now have 16 to 24 beds. Keeping all the necessary patient information current and documented, and performing all interventions safely in the midst of family members calling and other interruptions is challenging.

To optimize care in this hectic setting, the nurse needs to recognize the effects and side effects of various pharmacologic interventions, juggle the administration of multiple drugs, and decide about priorities during the bedside assessments to determine the outcome goals for the patient. This is no simple task, even for an experienced nurse.

Staffing Challenges

Challenges for bedside staff in sedation management include differentiating agitation from other conditions such as pain, standardizing the assessment of agitation, and obtaining multidisciplinary agreement about treatment interventions and priorities.

The signs and symptoms of agitation are fairly obvious. Descriptive terms commonly used include restlessness; thrashing around in bed; pulling at lines, tubes, and restraints; over-breathing the ventilator; and dysynchrony with the current ventilator settings. Vital-sign abnormalities such as tachycardia, tachypnea, and hypertension are common in an agitated patient. The need for assessment scales to move from the subjective terms associated with agitation to a standardized scale that can be used to manage sedation has been discussed frequently in the literature. The ideal scale should be simple to apply with clearly described grade changes between levels to allow clinicians to titrate sedation to the patient's condition. Although many scales and tools are available to monitor the degree of agitation, their utility to bedside staff in implementing treatment and intervention plans is not well understood.

Guidelines and standards of care have been developed to assist bedside staff with the challenges of sedative administration. However, follow-up studies have shown that implementation of these guidelines in bedside care has been less than satisfactory.

It is therefore important to consider the challenges facing nurses in the implementation of such guidelines.

A recent study showed that only about 20% of hospitals were able to implement daily wake-up assessments. Possible reasons for this include assessments not being performed, not being documented, or

not being identified in the electronic databases.

Even the question of when to perform an assessment can present major challenges. Should it be right before the patient is suctioned, while suctioning the patient, or five minutes after suctioning the patient? Which score is the one being sought for the assessment? And which score requires the nurse to intervene?

If a patient is asleep, calm and sedate when the nurse enters the room, that is an ideal sedation score. When a patient is repositioned in bed before being suctioned, how long should the nurse wait for the sedation score to return to the previous level before doing an intervention, administering a drug, or discontinuing a drug? Nurses are willing to do the different sedation assessments and to titrate interventions based on the scores, but they are not clear what exactly is expected of them at bedside, every minute, hour or day. For what portion of a 12-hour period are they supposed to maintain a patient at a particular assessment score? Is 70% of a 12-hour shift acceptable? Or should the goal be something else? Despite the shortcomings these questions suggest, protocol-driven intervention plans using agitation scales have been shown to improve patient outcomes such as duration of mechanical ventilation and length of stay in the ICU.

Other Factors

A few studies have addressed bedside decision-making issues. Other factors affecting sedative administration include staff attitudes and per-

ceptions of comfort, family member's perception of agitation, nurses' workload, and staffing ratios.

An ICU nurse often has to do several things at once during rapidly changing situations. The number of more senior experienced nurses who are thought of as being the mainstay in the ICU is dwindling. New, less experienced nurses often do not have the ability to do several things at once and still effectively use various protocols, assessment tools, and perform complex multidisciplinary interventions simultaneously. Training ICU bedside staff and maintaining experienced staff members at the bedside is a major issue.

Addressing Nursing Issues

Critical-care educators need to recognize the many complex issues associated with agitation, teach bedside staff the critical decision-making skills necessary to optimally manage

agitation, and facilitate the implementation of evidence-based practice strategies in bedside care. The newer type of assessments and interventions require a change in mindset and practice that does not happen overnight. Making these changes will require buy-in from nursing leadership management, and educators.

The multidisciplinary critical care community has made sedation management a priority in improving patient outcomes. National organizations including American Association of Critical Care Nurses, Society of Critical Care Medicine, and the Joint Commission on Accreditation of Healthcare Organizations have all recognized the need for standards of care for patients requiring sedation. These standards often overlap with other important standards such as those for pain management and the use of restraints. For the bedside nurse, the challenge is to incorporate all the required standards into a

patient-specific treatment plan that also includes strategies for efficient documentation of care. Electronic charting instruments, infusion pumps with real-time data acquisition systems, and medication administration logs may help improve efficiency.

Summary

Establishing a multidisciplinary standard of care for assessing, treating, and monitoring agitation in the ICU is imperative to optimize patient management and improve outcomes. All disciplines involved in the process need to recognize the nursing challenges and find new ways to make the bedside staff's work easier. Development of new technology to offset bedside practitioner workload and improve communication may help to address the challenging nursing issues related to the sedation of critically ill patients.

Daily Interruption of Sedation in Mechanically Ventilated Patients: The ICU Sedation Vacation

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Key Points

- *Sedation and pain control are important components of the treatment of mechanically ventilated patients.*
- *Directing treatment to specific and individualized goals will better assure that patient needs are met.*
- *Drug administration strategies based on principles of sedative pharmacology in critical illness should be used.*
- *Daily interruption of continuous sedative infusions can reduce many of the complications of sedation, including duration of mechanical ventilation and intensive care unit length of stay.*

Mechanically ventilated patients frequently suffer symptoms of subjective respiratory distress, and the majority receive analgesics and/or sedatives while they are undergoing mechanical ventilation. As experience with intensive care unit (ICU) patient outcomes has grown, our understanding of the complex pharmacology of sedatives and analgesics has increased. This has led to an awareness of the need for evidence-based protocols to guide the administration of sedatives to ICU patients.

Strategies for Delivery of Sedatives in Mechanically Ventilated Patients

Since no single drug can achieve all of the desired effects for sedation and pain control, using a combina-

tion of drugs, each titrated to specific endpoints, may be a more effective strategy. This approach can allow lower doses of individual drugs and reduce problems associated with drug accumulation. Both continuous infusion and intermittent boluses for intravenous drug administration have been advocated. Intermittent bolus administration of sedatives and analgesics may lead to fluctuations in level of sedation and increase demands on nursing time, which could take time away from other patient care issues. The perceived benefits of continuous sedative infusions include a more consistent level of sedation with better patient comfort. The convenience of continuous infusion for both patients and caregivers is likely the greatest reason for its popularity.

Strategies for sedation and analgesia in critically ill patients should ideally be based on pharmacokinetic and pharmacodynamic principles. Unfortunately, ICU patients often exhibit unpredictable responses to medications so that precise guidelines for drug administration for all patients are not possible. For example, when "short-acting" benzodiazepines such as midazolam and lorazepam are administered, they accumulate in tissue stores, which prolongs their clinical effect. Other factors that change the pharmacologic behavior of sedatives and analgesics include altered hepatic and/or renal function, polypharmacy with complex drug-drug interactions, altered protein binding, and circulatory instability. Therefore, titration of sedatives and analgesics against discernable clinical endpoints is the most common approach.

Further complicating the administration of sedatives in the ICU is the dramatic differences in the levels of sedation desired. Since over-sedated patients are easier to manage than under-sedated patients, clinicians may heavily sedate agitated patients. In the initial stages of critical illness, this is appropriate; however, main-

taining deep levels of sedation after patients are stabilized on mechanical ventilation can lead to the problems of prolonged sedation described above.

A daily assessment for organ failures should be routine for every critically ill patient. Assessment of end-organ perfusion and function is particularly important during the resuscitative phases of ICU care. Mental status examination is an important gauge of brain perfusion. Since brain injury is a devastating complication of critical illness, acute cerebral dysfunction must be detected quickly and corrected, if possible, before permanent injury takes place. Sedatives may interfere with neurological assessment.

Daily Interruptions of Continuous Sedative Infusions

Using a protocol for sedation has been shown to alleviate many problems. It can reduce the duration of mechanical ventilation, ICU and hospital length of stay, and the need for tracheostomy. Protocols assure adequate analgesia and sedation through frequent assessments of patient needs and goal-directed titration of analgesics and sedatives. A routine protocol of daily interruption of continuous sedative infusions can reduce many of the complications of sedation, including duration of mechanical ventilation and ICU length of stay. This strategy allows patients to spend some of their ICU time awake and interactive, potentially reducing the amount of sedative and opiate given, and reducing the need for diagnostic studies (e.g.,

brain CT scan) to evaluate unexplained alterations in mental status. Sedation protocols may allow the depth of sedation to be decreased without compromising the stated goals of sedation.

At first, the thought of decreasing or stopping sedatives in a critically ill patient who has been agitated may be unsettling. Clinicians may aggressively sedate patients early in their ICU course and then maintain the same level of deep sedation indefinitely. A daily break from sedatives can eliminate the tendency to “lock in” to a high sedative infusion rate that, while appropriate early in ICU care, may be unnecessary on subsequent days. When sedative infusions are decreased or stopped, tissue stores can redistribute drug back into the circulation. Interruption of sedative infusions may lead to abrupt awakening and agitation. This must be anticipated by the ICU team to avoid complications such as patient self-extubation. If excessive agitation is noted, sedatives should be resumed. Though attempts at awakening and communication may fail on a given day, this does not portend inevitable failure on subsequent days.

When awakening patients from sedation, for some the ideal may be to reach the brink of consciousness without precipitating excessive agitation. Once objective signs of consciousness are demonstrated, restarting sedatives *as needed* is reasonable. Restarting the sedative infusion at half of the previous dose also is reasonable. Adjustments from this starting point can be individualized to patient needs.

Reducing Complications

Studies of long-term consequences of recovery from respiratory failure and sedation are limited. Available data suggest that post-ICU depression is common in patients who require mechanical ventilation during critical illness. Post-traumatic stress disorder (PTSD) following recovery has also been reported. Some data suggest that lack of patient awareness about being sedated and/or their underlying illness is associated with development of PTSD, and that preservation of this awareness during mechanical ventilation may reduce this problem.

Previously, we reported how daily interruption of sedative infusions can reduce many of the complications of sedation in the ICU setting.¹ Patients who received either midazolam and morphine or propofol and morphine by continuous infusion were evaluated. The patients were managed by the primary ICU team and randomized to a group where there was a daily scheduled interruption of the sedative and opiate infusions or to a control group without a mandatory daily interruption.

In the interruption group, the duration of mechanical ventilation was reduced by 2.5 days and ICU length of stay was reduced by 3.5 days compared to the control group without interruption of sedative infusions. A significant reduction in diagnostic studies to investigate unexplained alterations in mental status was also noted. In the control group, 27% of patients underwent brain CT, brain MRI or lumbar puncture to investigate causes of mental status

changes; in the sedative-interruption group only 9% of patients underwent such studies. When diagnostic tests were done in these patients, the results were more often conclusive in the study compared to the control group. Only 25% of the patients in the control group had a test result that explained their mental status changes, compared with 50% of the patients in the sedative-interruption group. The patients in the sedative-interruption group averaged 86% of their ICU days awake and able to follow commands, compared with the control group, who averaged only 9% of their ICU days awake and able to follow commands. The amount of midazolam and morphine administered was also significantly reduced in the sedative-interruption group.

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

While it is clear that sedation protocols can improve patient outcomes, it is important to recognize that a treatment protocol is only a

guide and cannot address every clinical situation. Limitations of studies of the use of protocols include potential lack of generalizability (e.g., a single academic medical center may be different than a community setting), lack of blinding, lack of reporting of "other" outcomes such as long-term follow-up, and uncertainty about level of compliance needed to assure desired outcomes. A multidisciplinary, cooperative approach is necessary to assure compliance and successful implementation of protocols.

Summary and Conclusion

Sedation and pain control are important components of the treatment of mechanically ventilated patients. Directing treatment to specific and individualized goals will better assure that patient needs are met. All currently available agents for use in mechanically ventilated patients have limitations, and complications related to the use of these agents are common. Rather than seeking an ideal drug, drug administration strategies based on principles of sedative pharmacology in critical illness should be used. When these drugs are given to individual patients, establishing specific goals will allow the use of rational administration strategies, which should lead to improvement in both short- and long-term outcomes.

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ICU Sedation with Propofol: Measuring and Reducing Variation

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Key Points

- *Smart pump technology provides comprehensive continuous quality improvement (CQI) data that can identify medication safety issues for drugs given by the IV route.*
- *Although clinical practice guidelines for intensive care unit (ICU) sedation have been developed by the Society of Critical Care Medicine, in many settings they may not be consistently used.*
- *Propofol is a widely used, highly effective IV sedative for ventilator-assisted patients in the ICU.*
- *Our CQI data demonstrate overuse of propofol in these patients that may be associated with iatrogenic consequences not previously recognized.*
- *Preliminary analysis of outcomes and other clinical variables suggest that reducing the variability and doses of propofol has improved patient care and reduced treatment costs in patients with mechanical ventilation in the ICU.*

IV Medication Safety Systems: CQI Data

In October 2002 the St. Joseph's/Candler Health System (SJC) in Savannah, Georgia implemented a modular "smart" intravenous (IV) infusion system³ with safety software that incorporates a pre-defined set of dosing limits for infused medications commonly used in our hospitals. These limits are collectively known as Guardrails[®] limits and are designed to alert clinicians if a specific pro-

grammed dose of a medication is outside a minimum effective or maximum safe dose for the drug. Infusion cannot begin until the alert is addressed. The intent of the Guardrails[®] limits is to prevent medication errors. A total of 525 smart infusion systems were installed in our two tertiary-care referral hospitals. Each instance of a programmed dose less than or greater than the Guardrails[®] limits is electronically recorded as an "event" for continuous quality improvement (CQI) purposes.

SJC implemented smart IV infusion technology to improve the safety of medications with the highest potential to cause harm. Since implementation, event data have been accumulated in the computer "brain" for each device. All events are collected and saved by the system for future CQI analysis. These data have been synthesized for analysis of our initial experience with the safety software at SJC. The data indicate that most alerts were warnings of the possibility of drug overdose. The data also indicate that 7.2% of events resulted in the nurse canceling the administration process or resetting the pump (averted errors). These warnings involved multiple medications, including some of those identified by the USP from their MEDMARX[®] database as being associated with the highest liability for harm.¹

Smart IV infusion technology at SJC has provided a way to document actual drug administration activity at the bedside. The system allows us to identify and prevent medication errors, record pump programming steps that occurred before an intervention, record all actions taken by the nurse even if he/she continued the administration process after hav-

ing been “warned” that a pump programming instruction was outside of the guardrails limits, and implement corrective actions to reduce the potential for future medication errors.

Maintaining optimal comfort and safety for mechanically ventilated critically ill patients is an important goal. The Society of Critical Care Medicine (SCCM) has developed clinical practice guidelines to assist clinicians in the use of sedatives and analgesics for these patients (Table 1).² Indications for sedative agents are not well defined; nonetheless, they are commonly used adjuncts for the treatment of anxiety and agitation in the ICU.² Several drugs, including the benzodiazepines (diazepam, lorazepam, midazolam), propofol, and central-agonists (clonidine, dexmedetomidine), are used to sedate the mechanically ventilated patient.

Propofol Overuse

Among the commonly used agents, propofol (2,6-diisopropylphenol) has been favorably compared to the benzodiazepines, particularly midazolam, because it reduces the time needed for recovery of spontaneous respiration and successful weaning of patients from the respirator (Table 2).³⁻⁵ It has a rapid onset and short duration of sedation once discontinued.⁶ Propofol is available as an emulsion that provides 1.1 kcal/mL from fat and is an important caloric source for patients receiving a continuous infusion.⁷

Propofol is widely used in many ICU settings and is a convenient and efficient pharmacologic agent for

Table 1. ICU Sedation Guidelines²

- A sedation goal or endpoint should be established and regularly redefined for each patient; regular assessment and response to therapy should be systematically documented.
- The use of a validated sedation assessment scale is recommended.
- The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to minimize prolonged sedative effects.
- The use of sedation guidelines, an algorithm, or a protocol is recommended.

sedation and ventilator management because of its rapid onset and cessation of action. ICU nurses and physicians can titrate patients to a desired level of sedation with minimal concern for the potential of overdose or negative effects.

Serious adverse events can occur with propofol and include a number of metabolic,⁸⁻¹¹ neurologic,¹²⁻¹³ cardiac,¹⁴⁻¹⁶ infectious,¹⁷ pulmonary¹⁸ and

local reactions.⁷ Propofol can also cause anaphylactoid type reactions,¹⁹⁻²⁰ and tachyphylaxis²¹ has been documented.

In spite of the availability of clinical practice guidelines for the use of sedatives including propofol in the critically ill adult patient, our CQI data show that clinicians may administer this drug with insufficient concern for the quantity of drug infused per unit

Table 2. Propofol as an ICU Sedative³⁻⁵

- Highly lipophilic; extensively distributed in tissue; fat-solubilized emulsion
- Vd ≈ 60 L/kg
- Rapid action: 1-2 min; short duration after discontinuation
- Tri-phasic elimination process - t_{1/2} (α=1-8 min; β=1.5-12.4 hr; δ=26-32 hr) after infusion
- Serum conc for sedation: 0.14 - 1.90 mcg/mL constant infusion
- Dosing is weight dependent: 5-80 µg/kg/min range
- Tachyphylaxis can occur
- Expensive (≈ \$300/day/70-kg pt)

of time and for the potential occurrence of adverse events. Physicians routinely order this medication by indicating “Diprivan Drip,” “Titrate Diprivan,” or “Sedate with Diprivan.” In a 9-month period, the average dose of propofol was 100 mcg/kg/min for patients given continuous infusions. The recommended maximum rate of infusion for this indication is 80 mcg/kg/min when given for sedation of mechanically ventilated critically ill adult patients.²

Data from a national cohort of 52 hospitals where “smart” infusion devices are used suggest that our institution is not unique. Propofol is given using frequent bolus doses and administered at rates that exceed the upper limits of recommended dosing by the SCCM.²² CareFusion Pharmacy Services manages more than 180 acute care hospital pharmacies throughout the nation. Propofol ranks fifth among all purchases of pharmaceuticals in these hospitals despite the fact that it is available as a generic product. This would suggest that this drug is being used in large quantities in many institutions.²² It currently represents 81% of the expenditures for all IV sedatives used in these facilities.²³

Best Practice Improvements

In order to address the overuse of propofol at SJC a standardized ICU sedation order set was developed which incorporates SCCM good clinical practice guidelines for sedatives, analgesics, and neuromuscular blocking agents used in ventilator-assisted patients. The use of this order set and the accompanying

sedation management protocol is required at our institution. The protocol and order set requires physicians to prescribe a specific level of desired sedation for each patient dependent upon the physical condition and disease entity being treated. Nurses then dose propofol and/or other sedatives to maintain that level of sedation using the Motor Activity Assessment Scale (MAAS) sedation score.²⁴ Patients are given scheduled “sedation vacations” as appropriate to assess mental status.

Results

Data from our hospitals indicate that this change in process has dramatically improved how propofol is being used in our ICUs. Propofol dosing alerts from the infusion pumps have been reduced by greater than 50%; the number of reprogrammed doses after alerts, which indicate averted medication errors, has risen sharply. The number of bolus doses of propofol has been almost elimi-

nated. Preliminary data from an analysis of ventilated patients treated with propofol in the ICU before and after the implementation of the sedation protocol and order set is described in Table 3. Reductions in the total cost of drug, patient days on ventilators, and ventilator-associated pneumonia appear to be significant; however, further data collection and analysis is underway. Questions being addressed in our analysis include: Are there differences in outcomes among patients being treated with/without sedation guidelines in place? Are there differences in the number and type of guardrails alerts? And are there differences in the amount and cost of propofol administered?

Conclusions

Propofol is an important, potent, and expensive ICU sedative with an inherent potential for systemic, metabolic, neurologic and cardiovascular toxicity. CQI data from smart IV

Table 3. Changes after ICU Sedation Protocol Implemented

	Pre (n=208)	Post (n=163)
Propofol Use		
• Total Cost	\$1,774,395	\$650,399
• Cost per pt	\$8,531	\$3,990
Total Vent Days	2,912	1,283
Ave Vent Days	14.0	7.9
% with VAP	8.2%	5.5%
VAP Rate *	5.8	7.0

*VAP Rate = (VAP infections/vent days)*1000

infusion safety systems indicate that it frequently is dosed indiscriminately in many hospitals. Sedation should be more closely monitored by nurses and physicians with specific dosage titration using good clinical practice guidelines. CQI data from smart IV infusion systems can help to identify unrecognized problems with medication management that might be contributing to iatrogenic patient morbidity and mortality.

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PROCEEDINGS

Automation in Critical Care: Future Directions in Sedation Delivery

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Key Points

- *If not used carefully, medications being used for sedation can result in cycling between agitated and over-sedated states, over-sedation, and increased length of stay.*
- *If agitation is effectively controlled, over-sedation can be avoided.*
- *Consistent delivery of medications to control sedation provide better control of agitation compared with titration using subjective measures of patient response.*
- *Use of agitation level, not sedation level, as endpoint is a better approach to sedation management.*
- *The use of computer-assisted technology to improve titration of sedation based on changes in agitation level has been successful.*

The Problem of Sedation

Agitation interferes with therapeutic procedures and compromises safety of the patient and medical staff. Most sedation in intensive care is given to reduce agitation.¹ However, the use of drugs to control agitation may also compromise care.

The administration of medications for sedation is one of the most arbitrarily applied therapies in the intensive care unit (ICU), but there is little agreement on any particular method. As a result, practices and drug selection vary widely. The assessment of agitation is highly subjective and

dependent upon intuition and the experience of staff. Frequently there is concomitant use of many different drugs. Poor control of sedation can result in cycling between an agitated and sedated state, over-sedation, and increased length of stay.¹

To understand sedation management, it is necessary to understand the process of managing agitation. Recent literature has focused on clinical practice improvements through use of sedation-agitation scores^{1,2} and interruption of continuous infusions.

These approaches do not address the fundamental problem of agitation control, which is a drug-dosing

control problem best addressed by accurate measurement and understanding of the underlying dynamics.

The inability to effectively control agitation is an important factor associated with over-sedation. If agitation is controlled, over-sedation can be avoided. This eliminates the need for subjective sedation-agitation scores or interruption of sedation treatment.

Development of a Semi-automated Closed-loop Sedation Control System

A sedation management algorithm was developed that provided for simultaneous assessments of sedation and agitation.² Published scoring systems place agitation and sedation at either end of a linear scale.^{3,4} Critically ill, agitated patients, however, nearly always have a reduced level of consciousness that is indistinguishable from the effects of sedation. It is therefore impossible to select a single point on a linear scale that defines a patient's agitation-sedation state. This problem can be resolved by splitting the Riker Sedation-Agitation Scale⁴ into separate sedation and agitation scales (Table 1).

Table 1. Modified Riker Sedation-Agitation Scale⁴

Sedation scale	Agitation scale
-3 Unresponsive	+3 Dangerously agitated
-2 Responsive to tracheal suction or pain	+2 Moderately agitated
-1 Responsive to voice	+1 Mildly agitated
0 Calm and cooperative (or sleeping)	

Consistent delivery of sedation medications to all patients provides better control of agitation than titration of a number of drugs using widely variable subjective measures of patient response. Since there are no objective measures of agitation, a fixed mixture of drugs, such as morphine (1.0 mg/mL) and midazolam (0.5 mg/mL), and age-adjusted bolus sizes can be used for consistent sedation delivery.

Boluses of a fixed mixture of sedation drugs are given to reduce agitation using a Graseby 3500 syringe pump. The background infusion rate can be set as a proportion of the total amount of the drug combination given over the preceding 4 hours to control agitation. Only a portion of the background sedation is carried through to the next time period. As long as agitation is present, a background infusion is maintained. As the agitation diminishes, less sedation is required and the background rate is reduced accordingly.

The intention is to use agitation level, not sedation level, as the primary endpoint in sedation management. When mild agitation cannot

be tolerated (e.g., in severe head trauma), thresholds for treating agitation are reduced and an increased level of sedation is tolerated. In most cases, sedation is the useful side effect of treating agitation.

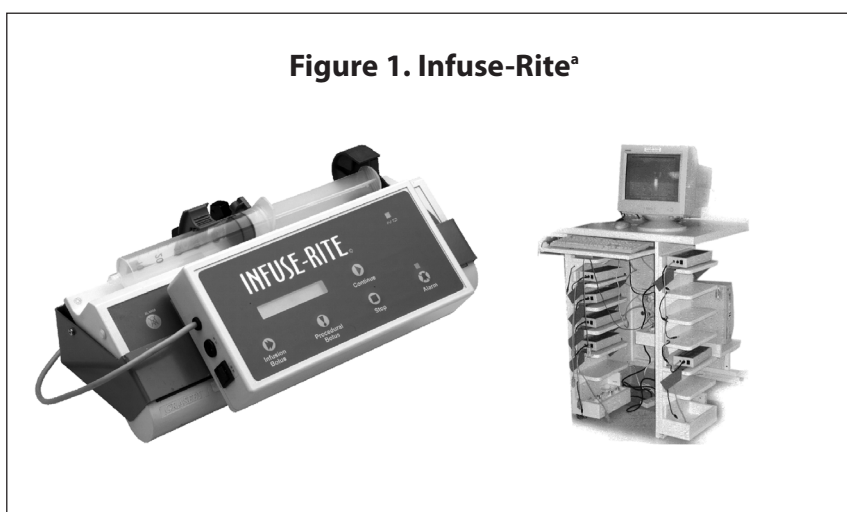
From time to time additional sedation is needed to provide anaesthesia to carry out uncomfortable or painful procedures. This differs from using the same drugs to reduce agitation. Feedback control of anaesthesia requires measurements of sedation and analgesia, whereas control of agitation requires measurements of

agitation response. Each therapy has a different clinical end point; hence, this additional sedation does not influence the background rate.

This algorithm has been successfully trialed using a paper flow chart. In virtually all cases, nursing staff readily titrated sedation to an acceptable and safe level of agitation.

Computerized Sedation Delivery Interface: The Infuse-Rite^a

A modification of the algorithm allowing hourly adjustments of the background infusion was incorporated into a simple user interface connected to the serial port of a Graseby 3500 syringe pump⁷ (Figure 1). Patient information (including weight for children less than 14 years) is uploaded to the Infuse-Rite using a personal computer (PC). Syringe labels are printed with the patient's name, hospital number and appropriate doses of morphine and midazolam that are weight-adjusted for children. The Infuse-Rite is then



Infuse-Rite mounted on Graseby 3500 syringe pump (left); the storage rack with PC used to input and retrieve data (right)

clipped onto the syringe pump and connected to its serial port. Nursing staff select “Infusion bolus” to control agitation or “Procedural bolus” to increase sedation for uncomfortable procedures. Each hour the previous hour’s drug dosage is displayed, which is recorded by nursing staff on a 24-hour chart. When sedation is ceased, the Infuse-Rite is reconnected to the PC and its drug administration data is downloaded. The drug delivery record is printed for the patient’s file and stored for auditing.

The Infuse-Rite provides a simple user interface allowing titration of sedation when there are changes in agitation level. Its success relates to ease of use, consistency in terms of simple input rules, and algorithmically determined outputs.

The rules are easily understood and the background infusion is continuously reduced in the absence of agitation, minimizing over-sedation. The use of agitation levels as clinical endpoints obviates the need for combined sedation-agitation scales.

Results

This approach has been successful, with nursing staff reporting high levels of satisfaction with regard to agitation-sedation control, patient and personal safety, and efficient use of time. Thirty nurses from the Christchurch Hospital ICU with more than 1 year’s experience were asked to participate in a survey comparing the computerized system with their previous experiences.⁶ The semi-automated sedation delivery system was rated higher in all areas: pain and discomfort, sedation control, agita-

tion control, time efficiency, ease of administration, patient safety, personal safety, and legal safety.⁶

Data from patients admitted to Christchurch Hospital ICU between March 2002 and October 2005 who were sedated using the Infuse-Rite were available for analysis. A total of 1070 patients who received sedation for more than 12 hours were included. Sedation doses are presented as milligrams of morphine. Midazolam consumption is half this value and omitted for clarity. Our data contain 120,141 boluses and infusion-rate changes to control agitation and nearly 36,000 additional boluses for procedures over 68,694 hours (7 years, 10 months). More than 156,000 doses or infusion adjustments were made without error. The Infuse-Rite was also highly adaptable and able to meet a wide range of demands. For example, one patient received 26 times more than the average dose (Table 2).

It is often felt that patients receive greater amounts of sedation at night to allow for sleep and rest, hence the early morning cessation of sedation

as described by Kress and colleagues.⁶ Our data show a significant reduction in drug administration around noon compared with mid-night ($p= 0.0133$).

We hypothesized that large variations in the cycling period of sedation delivery are an indicator of inconsistent sedation delivery and poor control. Specifically, large variations in the time period between peaks and troughs of sedation delivery are seen to indicate variability in consistency of care and hence poor control of agitation. The log of the maximum value of the peak-to-trough period is thus correlated with sedation duration, indicating that greater variability and poorer control contribute to prolongation of sedation time (Figure 2).

The linear relationship on the log scale indicates an exponential relationship between variability in delivery and sedation duration. This result highlights the potential importance of controlling this metric in any sedation delivery protocol. Thus, this result would indicate that sedation interruption routines are effective

Table 2. Administration of morphine via Infuse-Rite

Sedation method	Mean delivery (mg)	Max (mg)	Min (mg)	Hourly rate (mg/h)
Procedural boluses	36.2	950.0	0.0	0.6
Sedation background	136.8	3795.6	0.3	2.1
Sedation boluses	88.2	2103.0	0.5	1.4
Total sedation	261.2	6848.6	0.8	4.1

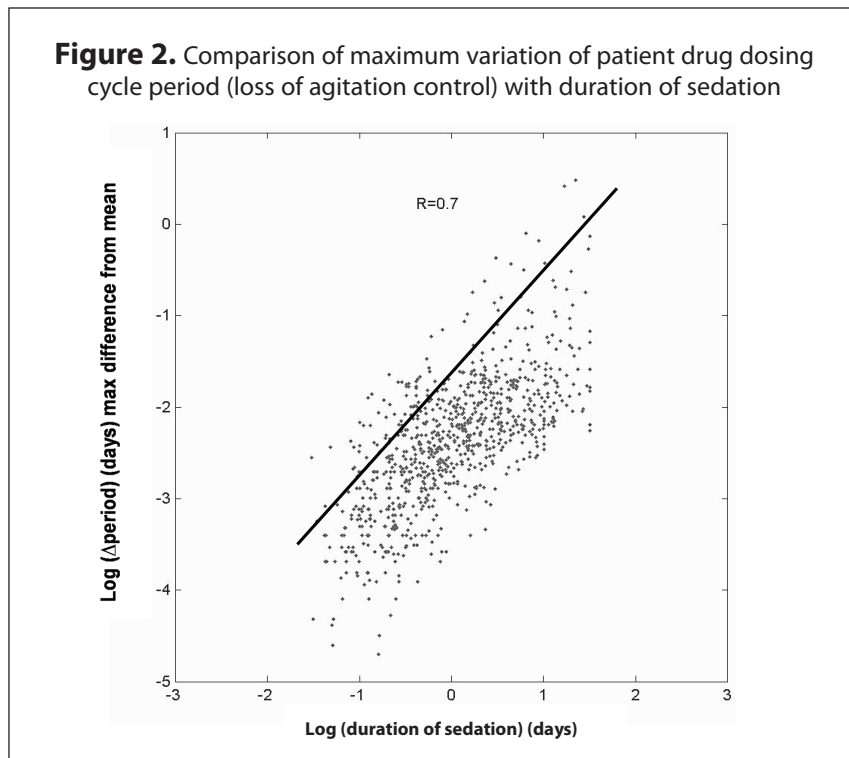


Figure 2. Comparison of the maximum variation of patient drug dosing cycle period (y-axis) and the duration of sedation (x-axis) for each of the 1070 patients. The natural log scale and resulting linear relationship indicates the linear exponential relationship between these variables. As the peak variability of sedation delivery cycling increases, hence loss of agitation control, sedation times increase.

primarily because they reduce delivery in situations of poor control.

Conclusions

Computerized sedation interface eliminates drug administration error and provides greater consistency and control of patient agitation. The Infuse-Rite algorithm with its goal of consistently weaning drug dose in the absence of patient agitation aims to minimize drug dose and over-sedation.

The use of the semi-automated Infuse-Rite controller still has limitations. In particular, assessment of agitation by clinicians is subjective and prone to error, while the controller's output uses fixed drug ratios and

parameters that almost certainly do not suit every patient. It also produces a slowly variable infusion rate with a fixed rate of variation, in spite of the fact that observed agitation dynamics are rapid and highly variable. The interface does provide high quality data and new insights into the dynamics of patient agitation.

Research should now focus on validating innovative and physiologically-based methods of optimizing sedation. This semi-automated controller provides consistency of sedation delivery, albeit with subjective and inconsistent inputs. In the future an ideal sedation controller would immediately respond to objective changes in agitation with timely,

appropriate boluses of sedation. This would provide a true, objective and physiologically-based feedback control system.

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PROCEEDINGS

Target-controlled Infusion: Introduction

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Key Points

- *Measurement of the plasma level of a drug is often used to individualize drug therapy, but drug concentration at the site of action is more important in determining patient response.*
- *It is very difficult to measure the concentration of a drug at the site of action (effect site) compared to the plasma and is not practical in the clinical setting.*
- *The apparent rate of drug flow into and from the site of action can be characterized by the time course of the drug effect.*
- *Pharmacokinetic modeling is one way to predict the concentration of a drug at the effect site, so that measurement of the concentration of the drug at that site is not necessary.*
- *Target-controlled infusion (TCI) technology uses pharmacokinetic modeling and calculations to predict drug concentration at the site of action and can rapidly achieve and maintain the desired predicted concentration.*
- *Clinicians can use TCI to improve the control of drug concentration at the site of action and clinical response.*

Target-controlled infusion (TCI) is widely used in Europe and potentially could be used in the United States, if cleared to market by the Food and Drug Administration. TCI is based on the use of pharmacokinetic modeling and calculations to control infusion to achieve a predicted concentration of drug. An understanding of the drug dose-response relation is essential to understanding TCI.

Drug Dose-response Relation

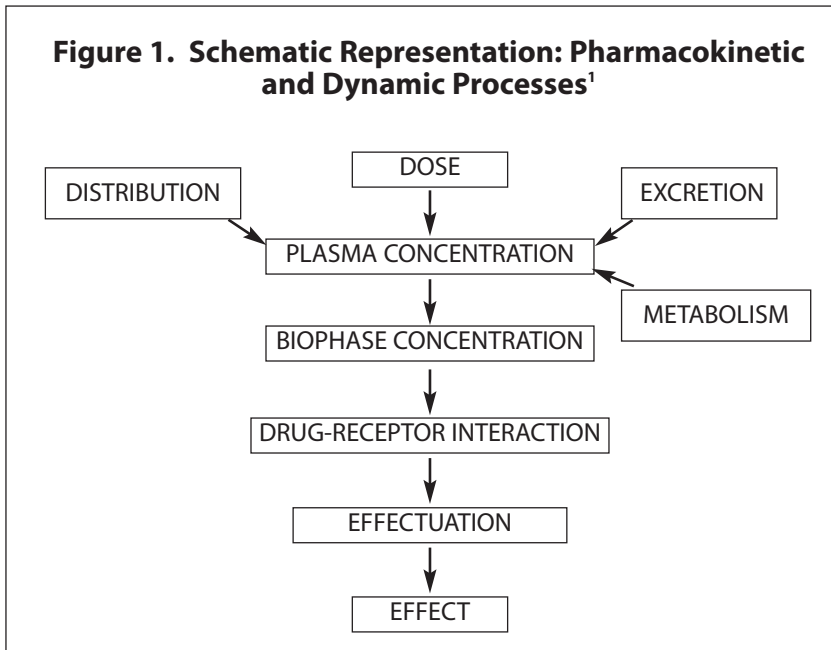
The dose-response relation can be divided into three parts: the relation between administered dose and plasma concentration (the pharmacokinetic phase), the relation between effector-organ concentration and clinical effect (the pharmacodynamic phase) and the coupling between pharmacokinetics and pharmacodynamics. The ultimate goal

when administering a particular dose of a drug is to obtain the desired clinical effect, for which a specific therapeutic concentration of the drug at the site of action (e.g., the receptor site or effect site) is necessary.

A drug interacts with a receptor and the pharmacological effect results. For most drugs, this effect-site concentration is not the plasma concentration, and the effect-site concentration is not measurable. By understanding the relation between the therapeutic plasma concentration and the clinical effect, however, it is possible to select a target concentration. This target concentration is defined as the plasma concentration that, on the basis of available information, is most likely to yield the desired effect.¹ Figure 1 shows the relationship between administered dose and resulting effect-intensity of a drug. Pharmacokinetic factors such as distribution, metabolism, and/or excretion determine the relationship between drug dose and effect-site drug concentration.

The above is also true for anesthetic agents: the drug-effect site is not the plasma,² and the concentration of the drug at the site of action is not measurable. The apparent rate of

Figure 1. Schematic Representation: Pharmacokinetic and Dynamic Processes¹



drug flow into and from the site of action can be characterized by the time course of the drug effect.³ The concentration at the site of action is called “the effect-site concentration,” and the corresponding compartment is called “the effect-site compartment.” The effect-site concentration is characterized by a temporal dissociation (or delay) compared with the plasma concentration. By knowing the effect-site concentration, this temporal problem can be overcome.³ Ultimately, the effect-site concentrations can be the same as the plasma concentration when equilibrated.

The effect-site concentration parallels the clinical effect of the drug. This means that the effect can be correlated with an effect-site concentration, which allows for a quantitative approach.

Many intravenous (IV) drugs are administered on the basis of dose per kilogram of body weight by means of

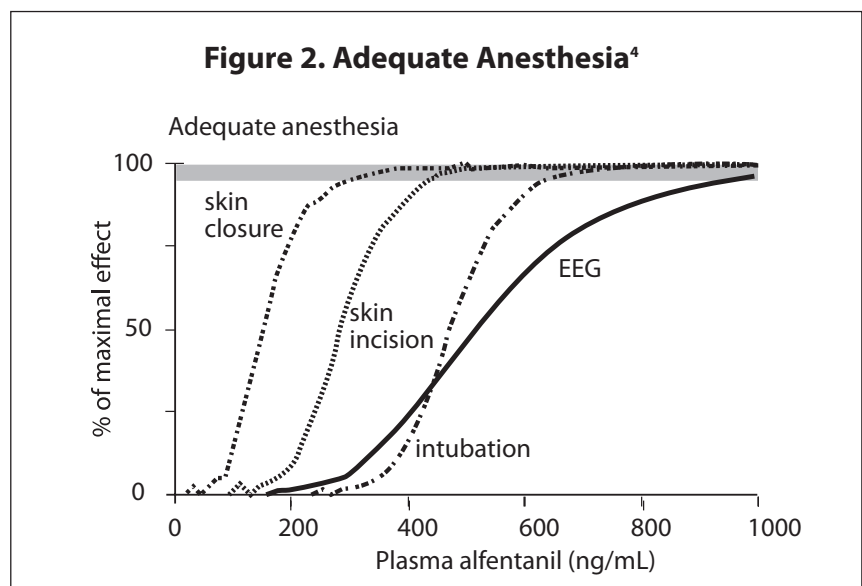
manually controlled infusion pumps. Measurement of either the plasma or the effect-site concentration of an IV drug is not currently possible. With the development of short-acting drugs, advanced computer technology, and a better understanding of patients' individual pharmacokinetics and pharmacodynamics, it has

been possible to develop accurate, computer-controlled, IV drug delivery systems for clinical use. Because of its direct relation to clinical effect, the effect-site concentration can be used to quantify the Ce50 (clinical effect is seen in 50 % of the patient population) or Ce95 (clinical effect is seen in 95 % of the patient population). For examples, see Figure 2.⁴

Target-controlled Infusion

Based on the pioneering work of Kruger-Thiemer⁵ and Schwilden et al.,⁶ TCI techniques use pharmacokinetic modeling and calculations to predict a set concentration in one of the pharmacokinetic compartments. TCI devices rapidly achieve and maintain a desired predicted concentration in the specific compartment. The specific target concentration is set after having evaluated the patient's clinical signs. When a certain concentration in the plasma compartment is targeted, this is called “open-loop plasma-controlled TCI.” When a certain concentration at the effect com-

Figure 2. Adequate Anesthesia⁴



partment is targeted, this is called "open-loop effect-site controlled TCI."

The use of TCI enables the clinician to continuously control the drug concentration in the plasma or at the effect-site, and to administer anesthetics according to their pharmacokinetic profile, without having to calculate the compartmental drug concentration on the basis of highly complex polyexponential functions. Instead of measuring the plasma or effect-site concentration (which is impossible *in vivo*), the computer-controlled infusion device predicts the drug concentration, which allows an anesthetist to dose an IV drug to a target plasma or effect-site concentration, instead of on the basis of dose per kilogram of body weight.

TCI infusion pumps can be used optimally only when three elements have been carefully established. First, the pharmacodynamic-pharmacokinetic model that controls the pump has to work accurately. Second, the pharmacokinetic parameters of a particular drug entered into the computer model have to match the pharmacokinetics of the patient. Third, the pharmacodynamics of the administered drug have to be well defined, in order for the anesthetist to attain the plasma concentration required for the desired effect.

Summary

The safe and effective use of rapidly acting drugs with a short duration of action will benefit from new technology that can target infusion

rates based on pharmacokinetic and pharmacodynamic characteristics of individual patients. TCI is such a technology, and has the promise of improving the use of anesthetics and analgesics if cleared for market use in the clinical setting by the FDA.

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Target-controlled Infusions for ICU and Procedural Sedation

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Key Points

- Clinicians new to target-controlled infusion (TCI) technology find it easy to use and soon develop a preference to it compared to manual control of infusion rates.
- When manual infusion regimens are used, there is a lengthy delay before a change in infusion rate results in a significant change in blood concentration and an even longer delay in effect-site concentration.
- With TCI systems, a proportional change in blood or effect-site concentration can be rapidly and accurately implemented.
- TCI systems enable both patient controlled analgesia and sedation to be accomplished safely.

Earlier generations of target-controlled infusion (TCI) systems provided the capability for clinicians to administer and adjust steady-state “target” blood concentrations of a drug. Since then it has been recognized that there is a time delay before equilibration occurs between the concentration in the blood and at the site of action (the “effect-site”) of the sedative and anesthetic agents. Objective measures of drug effect, such as parameters derived from an electroencephalogram (EEG), provide indirect assessments of the time-course of blood-effect-site equilibration, and allow the calculation of a blood–effect-site equilibration rate constant. By using this rate constant and iterative mathematical

processes, newer generations of TCI systems have been able to implement effect-site-concentration targeting.

This (blood- or effect-site-concentration targeting) does not mean that TCI systems offer a sedation or anesthetic on-off switch (i.e., the clinician selects an “appropriate” target concentration and the pump does the rest). One reason is that these systems rely on pharmacokinetic models to calculate infusion rates and estimate blood and effect-site concentrations. The estimated concentrations may not be accurate, because there is considerable variability in the way that patients distribute and metabolize drugs. More importantly, there is a very large vari-

ability in pharmacodynamic sensitivity among patients. An inadequate blood concentration for one patient may be excessive for another. Titration of dose (estimated blood concentration) to clinical effect is always required. Therefore, there are several compelling reasons to recommend the use of TCI systems for procedural and ICU sedation.

Ease of Use

Anesthesiologists new to TCI technology find it easy to use, report that the systems make it easy to adjust the depth of anesthesia, and soon develop a preference for TCI systems over manual control of infusion rates.¹ This is probably the major reason why in the United Kingdom and most of Europe, the majority of anesthesiologists administering total intravenous anaesthesia use a TCI system.

TCI use in the ICU environment is not as widespread as in the operating room. McMurray and colleagues reported the outcome of a multi-centre study of the use of propofol TCI systems for ICU sedation in 122 patients.² In the vast majority of patients the clinicians reported that ease of control of sedation was “good” or “adequate.”

Steady-state Blood Concentrations, Assessment of Treatment Efficacy

By definition, TCI systems provide steady-state blood (or effect-site) concentrations. This makes possible rapid and rational assessment of efficacy of the administered dose (target concentration), particularly when effect-site targeting is used. By contrast, assessment of treatment efficacy is more difficult when manually controlled infusions are used. When current agents are administered at a fixed infusion rate, there is a long (and variable) delay before anything approaching a steady-state situation is reached (Figure 1). For example, if fentanyl is infused at a fixed rate, the blood concentration will rise steeply for 24 hours and only reach steady state at 48 hours. A single, fixed infusion rate may provide inadequate sedation for a time, adequate sedation for a subsequent period, and finally excessive sedation.

How and when should a clinician assess the adequacy of a dose or guess an appropriate dose or infusion rate for an individual patient? To properly assess the efficacy of a change in infusion rate, the clinician should wait until a new steady state is reached, but for many sedative, hypnotic and analgesic agents this is not practical, because of the long delays before new steady states are reached. If changes are made before steady-state concentrations are reached, then over- and under-shooting of the blood concentrations are likely.

Speed and Accuracy of Titration

In the ICU and during procedural sedation, rapid changes (increases or decreases) in blood and effect-site concentrations of sedative and analgesics are often required. For example, increases might be required for tracheal toilette, removal of surgical drains or physiotherapy, while

decreases might be necessary after such procedures, or in a patient who has become apnoeic or developed cardio-vascular instability as a result of excessive administration.

When manual infusion regimens are used with current agents, there is a lengthy delay before a change in infusion rate results in a significant change in blood concentration (Figure 2) and an even longer delay before this results in a significant change in effect-site concentration. Moreover, during the first few hours of infusion of agents such as propofol or fentanyl (when blood concentrations are rising steeply), the blood concentration may continue to increase despite small decreases in the infusion rate.

When rapid increases are required, most clinicians using manually controlled infusions administer a bolus dose. The size of a bolus dose is difficult to judge - if it is too small, the effects will be inadequate; if it is too large, then the resulting large increase in blood and effect-site concentrations may cause serious adverse effects. At commonly used concentrations of current sedatives and analgesics, fairly small bolus doses generally are required.

TCI systems can overcome all these difficulties. They can produce almost step-wise increases in concentrations, by automatically administering a bolus (a rapid infusion, with the rate and duration accurately calculated), followed by step-wise decreases in infusion rate. When a decrease in target concentration is required, TCI systems produce the

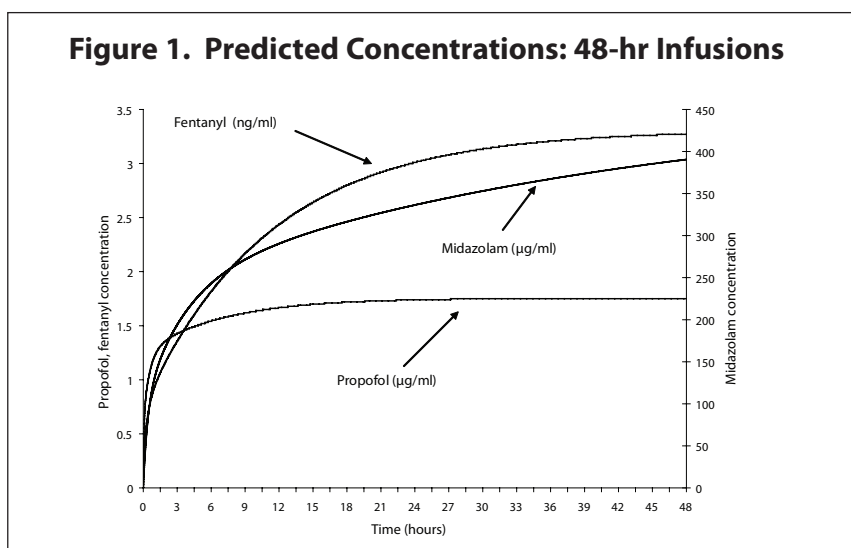


Figure 1. Simulation showing predicted concentrations resulting from 48 hours infusions of propofol (200 mg/hr), fentanyl (100 µg/hr) and midazolam (10 mg/hr)

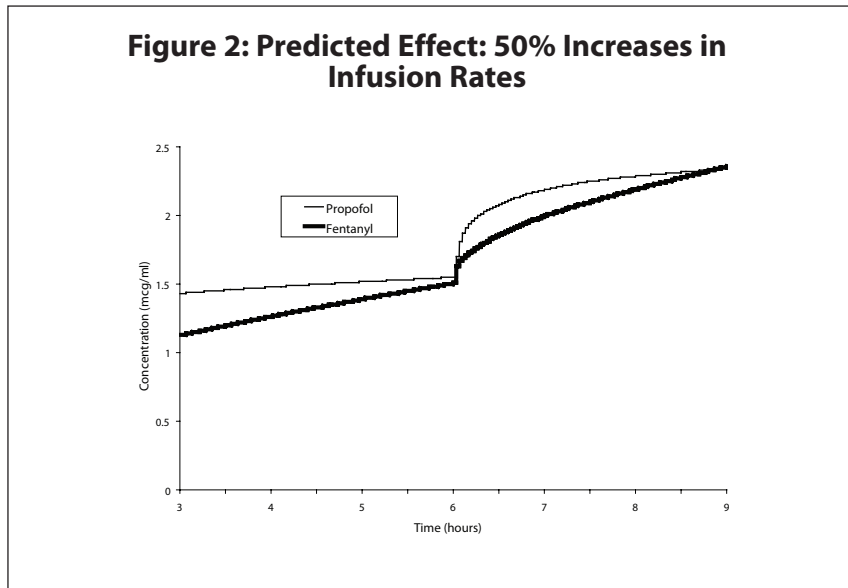


Figure 2. Simulation showing the predicted effect of 50% increases in the infusion rates of fentanyl (infused at 100 µg/hr for 6 hours, and at 150 µg/hr thereafter, predicted concentrations based on Shafer model) and propofol (infused at 200 mg/hr for 6 hours and at 300 mg/hr thereafter, predicted concentrations based on Marsh model). Note that it takes many hours for the blood concentrations to increase by 50%.

most rapid possible fall by switching off the infusion until the new target concentration is achieved. Although it is feasible for a clinician to temporarily switch off a manually controlled infusion, this is generally unwise, because if he or she forgets to restart the infusion, then further problems may arise from inadequate dosing.

With TCI systems, proportional changes to the blood or effect-site concentration can be rapidly and accurately implemented. Although measurement of the blood concentration in an individual may reveal a large difference from the target concentration, this does not matter. If the target concentration is changed, the achieved (measured) concentration will change by the same proportion, facilitating rational assessment of the impact of the change.

Cardiovascular Stability

When compared with manually controlled infusions, TCI systems have been shown to be associated with equivalent or improved cardiovascular stability in patients undergoing general anesthesia.^{1,3-7} The chief reason is that when TCI systems are used for induction, the infusion rates and total doses are lower than those used by anesthesiologists (who tend to be impatient and administer boluses at rates far greater than the maximum infusion rates of the TCI systems). At present there is little evidence that TCI systems are associated with improved cardiovascular stability during procedural or ICU sedation.

Patient-controlled TCI Systems for Analgesia and Sedation

Studies of patient-controlled-analgesia systems have shown that

patients prefer to have control over the administration of their analgesics. In recent years several groups have developed patient-controlled-sedation systems. With currently available agents, sedation systems that administer a bolus are unlikely to be successful, because they result in large fluctuations in blood concentrations with the potential for adverse outcomes resulting from troughs of excessively low concentrations and peaks of excessively high concentrations.

Patient-maintained-analgesia and -sedation systems combine the benefits of patient control with TCI technology. With these systems, a patient demand (using a handset or other means) made outside of a lockout period will result in a pre-defined increase in the target concentration. If no further demands are made, the system maintains the blood concentration at the current target concentration for a pre-set period of time, and then slowly reduces the target concentration to maintain safety.

Studies of the use of these systems for analgesia and sedation show that they are safe and effective, and that patients like using them.⁸⁻¹⁸ A recently completed study compared patient-maintained sedation (PMS) with anaesthesiologist-administered sedation, and showed that PMS was associated with less hypotension and oversedation.¹⁹

Accuracy of TCI Systems

Accuracy of TCI systems sometimes concerns clinicians unfamiliar with them. The chief benefit of TCI systems is that they administer steady-state blood concentrations

rather than exact concentrations. Even if 100% predictive accuracy were achieved, titration to effect would remain necessary to accommodate the large inter-individual variability in pharmacodynamic sensitivity among different patients to most sedative and analgesic agents.

A TCI system administers a drug infusion at rates determined by a model derived from studies of the pharmacokinetics of a drug in a population of patients or subjects. Thus, the concentration shown on the user interface is only an estimate. Varvel and colleagues have proposed a set of standard criteria for assessing the predictive performance of computerised infusion pumps.²⁰ These criteria are median performance error (MDPE), a measure of bias or offset; median absolute performance error (MDAPE), a measure of inaccuracy or imprecision; wobble, a measure of the intra-individual variability in errors; and divergence, a measure of any trend over time in the size and magnitude of errors. For computer-controlled infusion pumps a MDPE (bias) of 10% to 20 % and a MDAPE of 20% to 40 % have been proposed as acceptable,²¹⁻²² and most of the commonly used models perform well within these limits.

Many factors can influence the actual drug concentrations achieved. The models in use were usually derived from studies in healthy patients. Critically ill patients suffer many physiological derangements that have the potential to alter drug distribution and metabolism compared to healthy patients. For exam-

ple, critically ill patients suffer alterations in regional blood flow including reduced hepatic blood flow, causing impairment of hepatic function. Simulations show that large changes in the compartment volumes produce relatively insignificant changes in model performance, generally resulting in a short-lived overshoot following a target increase. Large decreases in metabolic and distribution clearance rates, however, can cause significant, sustained errors.

There are few data about the performance of current pharmacokinetic models used in the critically ill. McMurray found that for propofol, clearance was almost normal and the values for bias and inaccuracy were very similar to those found in healthy adults.² Cavaliere has shown that hypoalbuminemia has little effect on propofol pharmacokinetics,²³ and Servin showed that the pharmacokinetics of propofol (given by infusion) were not markedly altered in patients with cirrhosis.²⁴ Thus, for propofol there is little evidence at present to suggest that model performance in the critically ill is significantly worse than in healthy patients. Further studies are needed to assess the accuracy of the existing pharmacokinetic models for other agents commonly administered by TCI such as remifentanyl and alfentanil.

Conclusions

TCI systems administer steady-state blood drug concentrations by constantly adjusting the infusion rate (to take account of the reduced redistribution loss from the central compartment as time goes by). They

enable rapid and precise titration of drugs used for sedation, anesthesia and analgesia, and rational assessment of the impact of any changes in dose. In healthy patients, the performance accuracy for commonly used drugs and models is acceptable, and current data indicate that the performance accuracy for pharmacokinetic models for propofol is likely to be similarly acceptable in critically ill patients. TCI systems do not provide an "on-off" switch for sedation and analgesia, but do provide a more rational method of administering these drugs.

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PROCEEDINGS

Physiology of Oxygen and Carbon Dioxide Monitoring

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Key Points

- Oxygenation is vitally important in the management of post-operative patients and those being sedated for procedures.
- Pulse oximetry does not give enough forewarning of hypoxia to implement timely corrective action.
- Capnography is a reliable monitor of ventilation that can be used to monitor pain management in post-operative patients and sedation for procedures.
- The use of pulse oximetry and capnography should allow patients to be treated with opiate analgesics and sedatives with less risk of undetected catastrophic respiratory events.

oxygenation and detects hypoxia. However, it does not give enough forewarning to implement corrective measures to prevent hypoxic consequences. This is easily understood based on the relationship between arterial oxygen tension (PaO₂) and oxygen saturation (SpO₂) (Figure 2).

The SpO₂ does not begin to decrease from 98-100% until PaO₂ decreases below 100 mmHg. Decreases in PaO₂ below 80 mmHg are associated with dramatic decreases in SpO₂. This is because of 'S'-shaped relationship between SpO₂ and PaO₂. The decreases in SpO₂ can be exaggerated with clinical conditions associated with a

Among many complications that are of concern in the postoperative period, oxygenation assumes a vitally important place in the management of any postoperative patient. This becomes all the more important when pain relief medications are used to control postoperative pain. Many pain relief medications result in respiratory depression and consequent hypoxia (Figure 1). Hypoxia, if unrecognized, leads to unexpected postoperative disaster with medico-legal implications. Therefore, post-operative monitoring becomes mandatory for patients who are receiving pain medications that can depress cardio-respiratory systems.

Clinical Determination of Oxygenation

A pulse oximeter is an excellent and reliable device that monitors

Figure 1. Potential Post-operative Complications

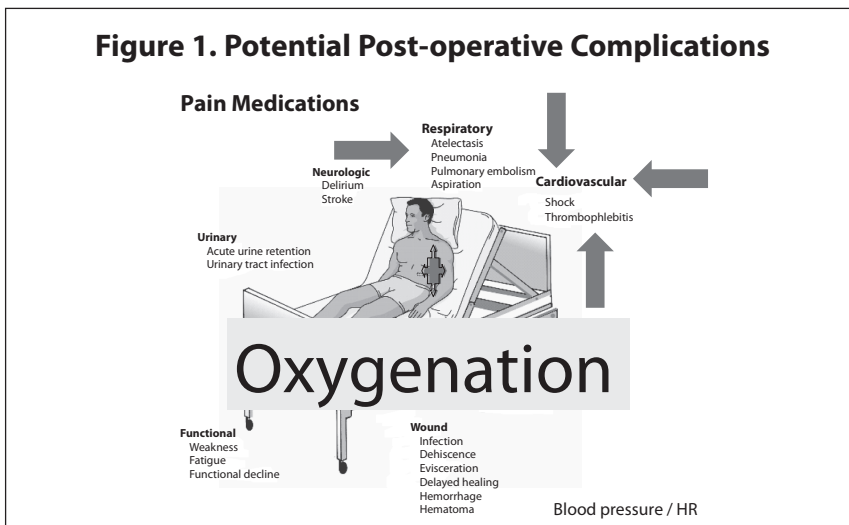
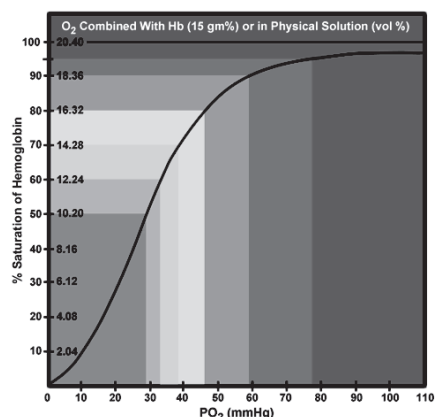


Figure 2. Relationship Between PaO₂ and SpO₂

Pulse Oximetry



reduction in functional residual capacity (FRC) that acts as the oxygen reserve buffer in the lungs. Obesity is a classic example, and FRC is known to decrease following abdominal surgeries even in normal-weight individuals.

The time interval from impending hypoxia to actual hypoxia is decreased with decreased FRC, and this decreased time may not be sufficient enough to call and initiate corrective measures to prevent hypoxia from occurring. Apart from stable hemodynamics, ventilation is a major determinant of oxygenation. Hence, it is necessary to monitor ventilation to detect episodes of inadequate or decreased ventilation that may result in hypoxia, if uncorrected. This way, one could avoid potentially life-threatening episodes in the postoperative period, when the monitoring of vital signs is not as frequent as in the operating room or in the postoperative anesthesia care unit (PACU).

Capnography has been shown to be a reliable monitor of ventilation in

the operating room. Its use is being extended into many areas outside of operating rooms to monitor ventilation in patients undergoing a variety of invasive and non-invasive surgical and medical procedures. These areas include intensive care units, emergency rooms, interventional radiology suites, gastroenterology suites, interventional cardiology units, and pre-hospital settings such as air and emergency ambulance services. It is only a question of time before capnography in association with pulse oximetry will be used to monitor postoperative patients receiving postoperative pain medications via intravenous route.

Overview of Physiology of Capnography

Carbon dioxide (CO₂) is produced in the tissues and diffuses into the venous blood, which reaches the right side of the heart and reaches the lungs via pulmonary circulation. Here oxygen (O₂) enters the blood and carbon dioxide (CO₂) is eliminated during expiration. CO₂ is typically

measured at the mouth, nose, or at the junction between the endotracheal tube and ventilator circuit.

At the end of inspiration, assuming that there is no rebreathing, the airway and the lungs are filled with CO₂-free gases. Carbon dioxide diffuses into the alveoli and equilibrates with the end-alveolar capillary blood (PaCO₂ = P_cCO₂ = 40 mm Hg). The actual concentration of CO₂ in the alveoli is determined by the extent of ventilation and perfusion into the alveoli (V/Q ratio). The alveoli with higher ventilation in relation to perfusion (high V/Q alveoli) have lower CO₂ compared to alveoli with low V/Q ratio that would have higher CO₂. As one moves proximally in the respiratory tract, the concentration of CO₂ decreases gradually to zero. The volume of CO₂-free gas is termed “respiratory dead space” and here there is no exchange of O₂ and CO₂ between the inspired gases and the blood. As the patient exhales, a CO₂ sensor at the mouth will detect no CO₂ as the initial gas sampled will be the CO₂-free gas from the dead space. As exhalation continues, CO₂ concentration rises gradually and reaches a peak as the CO₂-rich gases from the alveoli make their way to the CO₂ sensing point at the mouth. At the end of exhalation, the CO₂ concentration decreases to zero (base line) as the patient commences inhalation of CO₂-free gases. The evolution of CO₂ from the alveoli to the mouth during exhalation, and inhalation of CO₂-free gases during inspiration gives the characteristic shape to the CO₂ curve, which is identical in all humans with healthy

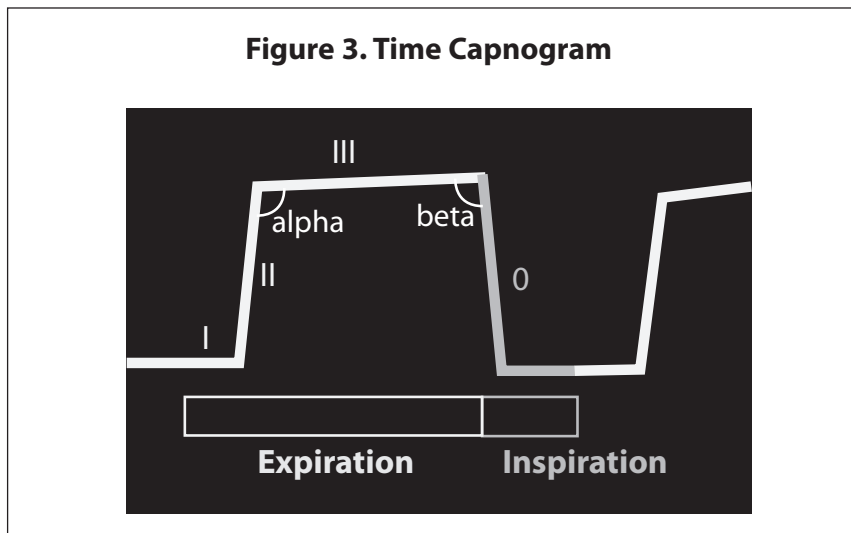
lungs. Any deviation from this identical shape should be investigated to determine a physiological or a pathological cause producing the abnormality.

Time Capnograms

A time capnogram can be divided into inspiratory (phase 0) and expiratory segments (Figure 3). The expiratory segment, similar to a single breath nitrogen curve or single breath CO₂ curve, is divided into phases I, II and III, and occasionally, phase IV, which represents the terminal rise in CO₂ concentration. The angle between phase II and phase III is the alpha angle. The nearly 90-degree angle between phase III and the descending limb is the beta angle. For more details on this section: please refer to www.capnography.com terminology section.

The CO₂ concentration reaches a maximum at the end of exhalation. This maximum concentration is called end-tidal carbon dioxide concentration or tension depending on whether it is expressed in fractional concentration or mm Hg. End-tidal carbon dioxide reflects CO₂ concentration of alveoli emptying last. The normal values of EtCO₂ are around 5% or 35-37 mm Hg. The gradient between the blood CO₂ (PaCO₂) and exhaled CO₂ (end tidal CO₂ or PetCO₂) is usually 5-6 mm Hg. PetCO₂ can be used to estimate PaCO₂ in patients with essentially normal lungs.

The three major determinants of CO₂ waveform are cardiac output, ventilation, and CO₂ production. Hypermetabolic states such as thyro-



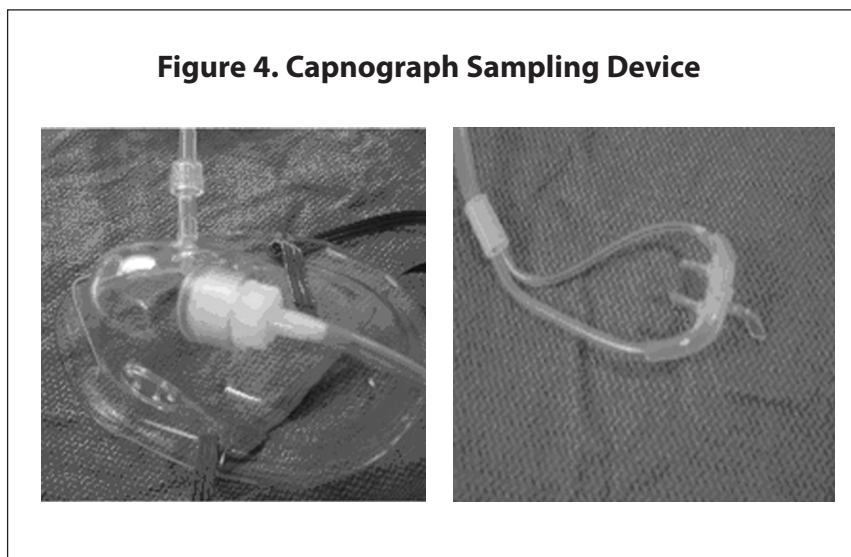
toxicosis or malignant hyperpyrexia are associated with increased CO₂ production and therefore with higher end-tidal CO₂.

Capnography Sampling Devices

Capnography not only detects abnormalities in ventilation perfusion, such as those resulting from COPD or bronchial asthma, but also monitors PaCO₂ indirectly. If the sampling of end-tidal gas is ade-

quate, hypercarbia can be detected from capnography monitoring. In addition, capnography displays abnormal respiratory patterns that may suggest inadequate or depressed ventilation. Adequate sampling can be ensured by several methods and sampling devices (Figure 4).

The capnograms from good sampling devices appear similar to conventional capnograms obtained via endotracheal intubation. However,



dilution of expired gases is unavoidable in certain circumstances. Under these conditions, a change from baseline should forewarn of respiratory depression or at least should encourage a clinician to investigate the change in capnograms.

Summary

An understanding the physiology of oxygenation and ventilation should make it apparent that it is quite logical to monitor not only oxygenation but also ventilation in post-operative patients receiving narcotics for pain relief. Capnography has been used successfully in gastroenterology sedation procedures to detect inadequate respiratory events well before the changes in oxygenation. Using combined technology should allow patients to recover safely in the potentially turbulent postoperative period, without being subjected to the risk of undetected catastrophic respiratory events.

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Center for Safety and Clinical Excellence Sixth Conference

Sedation Therapy: Improving Safety and Quality of Care

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