SEDATION AND ANALGESIA TECHNIQUES:
The Changing State of the Art & Science

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CME/CE Activity
Release Date: November 30, 2009
Expiration Date: November 29, 2010

Sponsored by
Boston University School of Medicine

Supported by
an educational grant from Eisai Pharmaceuticals

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NEEDS ASSESSMENT

Moderate sedation is a state of sedation/analgesia in which the patient is able to respond purposefully to verbal or tactile stimulation; this approach may combine elements of local/regional anesthesia and IV medications—and provides faster recovery than general anesthesia.1

Key issues in the administration of moderate sedation/analgesia include:

• Determining the proper dosage for a specific level of sedation in spite of the wide variability in patient drug response.
• Understanding the pharmacokinetics, incremental dosing, and synergistic effects of various agents, and recognizing and responding promptly to any adverse drug effects.
• Preventing oversedation, which may lead to respiratory depression or airway obstruction.

Oversedation is the primary morbidity associated with sedation/analgesia, one that can be minimized through appropriate use of monitoring and early resuscitation.2

The choices of agents to use in procedures requiring sedation are expanding. Fospropofol disodium was approved by the United States Food and Drug Administration (FDA) in December 2008 for use in monitored anesthesia care in adults undergoing diagnostic or therapeutic procedures. In clinical trials, fospropofol was found to provide safe and effective sedation for patients undergoing flexible bronchoscopy, colonoscopy, and other procedures.3

Dexmedetomidine is an α₂-adrenergic agonist with hypnotic, sedative, sympatholytic, and analgesic properties that reduces anesthetic and opioid requirements. Because dexmedetomidine does not generally cause respiratory depression, and patients can be easily aroused, it may be used for sedation and analgesia for various procedures, including awake tracheal intubation.4 It was originally approved in 1999 for continuous IV sedation of immobile and mechanically ventilated patients in the intensive care setting for up to 24 hours.5 In October 2008, dexmedetomidine received an additional indication from the FDA for use in nonintubated patients who require sedation prior to or during surgery and other procedures.6

Additional technologies being studied include computer-assisted personalized sedation (CAPS) and patient-controlled analgesia/sedation. One form of CAPS currently seeking FDA approval is designed to help deliver minimal to moderate sedation with propofol during endoscopy, monitoring six sedation parameters. The device has been reported to work well when operated by an endoscopist/nurse team during colonoscopy and other such procedures.7

One of the controversial issues with the use of propofol and now fospropofol for sedation is which health professionals should provide and monitor sedation during diagnostic and therapeutic procedures, and what qualifications are necessary.8 The American Society of Anesthesiologists states that the provider of moderate sedation “must be prepared and qualified to convert to general anesthesia when necessary.”9

In contrast, a joint statement by three gastroenterologic societies states that moderate sedation can be performed safely on “average-risk” patients in “diagnostic and uncomplicated therapeutic endoscopy and colonoscopy” without the routine assistance of an anesthesiologist or an anesthetist.10 Similarly, the Society of Gastroenterology Nurses and Associates has stated: “Registered nurses trained and experienced in gastroenterology nursing and endoscopy can administer and maintain moderate sedation and analgesia (conscious sedation) by the order of a physician.”11

As new, more efficient methods of sedation development and gain acceptance, it is increasingly important for clinicians who are involved in providing or monitoring sedation to keep abreast of the scientific advances that are occurring in the field.

REFERENCES


TARGET AUDIENCE

Anesthesiologists and nurse anesthetists

LEARNING OBJECTIVES

At the conclusion of this program, clinicians should be better able to:

• Define the concept of sedation and analgesia techniques and the spectrum of clinical scenarios to which they apply
• Describe specific practical applications of sedation and analgesia techniques in diagnostic and therapeutic procedures, focusing on those that require moderate sedation
• Cite the latest safety and efficacy data on agents and combinations of agents used to achieve sedation/analgesia during diagnostic and therapeutic procedures
• Identify emerging agents and/or technologies used to achieve and monitor sedation/analgesia
• Summarize current guidelines on the appropriate use of sedation and analgesia techniques and the respective roles of health professionals performing the procedure and monitoring the patient

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Program Code: E.SAMBAHAY09
Release Date: November 30, 2009; Expiration Date: November 29, 2010

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Keith A. Candietti, MD, receives grant/research support from Eisai Pharmaceuticals, Hospira, Pfizer Inc., Cadence, Stryker, and Schering-Plough Corporation. He is a consultant for Eisai Pharmaceuticals, Hospira, Pfizer Inc., Cadence, and Schering-Plough Corporation and is on the speakers’ bureaus for Eisai Pharmaceuticals, Hospira, and Pfizer Inc.
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Rafael A. Ortega, MD (Course Co-Director), has nothing to disclose.
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Cover photo and photo, page 4: Photo Researchers, Inc.
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TABLE of CONTENTS
Introduction 4
Getting started 5
Available agents 7
Propofol administration 11
On the horizon 12
Conclusion 13
References 13
CME/CE Post-test 15
Program Evaluation and Answer Sheet 16
Procedures that routinely use sedation include colonoscopy, bronchoscopy, endoscopic ultrasound (EUS), esophagastroduodenoscopy (EGD), and endoscopic retrograde cholangiopancreatography (ERCP). Sedation is also employed in a host of oral and maxillofacial procedures, most commonly tooth extraction. In addition, it is used in plastic surgery, biopsies, cataract surgery, and other medical procedures.

The American Society of Anesthesiologists (ASA) depicts the various levels of sedation as a continuum, a concept that emphasizes the tendency of patients to move fluidly from one level to the next. Individual patient response to sedation agents can vary significantly depending on a host of factors. Practitioners must be aware of and ready for patients to move from one sedation level to another, particularly a deeper, unintended level during a procedure. Therefore, practitioners delivering sedation must be trained and skilled in rescue techniques, including appropriate use of reversal agents, managing airways, and providing advanced cardiac life support.

ASA guidelines detail four levels of sedation (Table 1):

1. **Minimal sedation/anxiolysis** refers to a state during which patients respond normally to verbal commands; cognitive function and coordination may be impaired; ventilatory and cardiovascular functions are unaffected.

2. **Moderate sedation/analgesia** (formerly called conscious sedation) is a depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation (reflex withdrawal from a painful stimulus is not considered a purposeful response). No
Interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep sedation/analgesia is a depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

For the overwhelming majority of endoscopic and many oral procedures, moderate sedation provides sufficient comfort, anxiolysis, and pain relief. Moderate sedation is thought to be safer than deep sedation and meets the patient’s desire for a rapid recovery and return to everyday activities. Because many moderate-sedation regimens are administered by non-anesthesiologists, including gastroenterologists, trained nurses, emergency physicians, and oral and maxillofacial surgeons, this approach is widely used in the United States. As detailed later, the issue of non-anesthesiologists delivering some forms of moderate sedation is highly controversial.

Clinicians who administer sedation must strike a balance between under- and oversedation. If patients are underdated, they can experience adverse effects such as agitation, hypertension, tachycardia, myocardial ischemia, and wound dehiscence. The patient also may injure himself or clinical staff.

In contrast, an oversedated patient may suffer from loss of airway, hypotension, desaturation, ischemia, and delayed recovery. Of the two problems, oversedation generally poses greater risk and consequences.

In 2006, Bhananker et al identified the risks involved by reporting on liability claims from the ASA’s Closed Claims Database that were related to monitored anesthesia care (MAC). The ASA defines MAC as “a physician service which is clearly distinct from moderate sedation due to the expectations and qualifications of the provider who must be able to utilize all anesthesia resources to support life and to provide patient comfort and safety during a diagnostic or therapeutic procedure.”

The study revealed that respiratory depression caused by oversedation was a major factor in MAC injuries, representing the specific damaging mechanism named in 21% of claims. Of note, 18% of MAC claims were for hypoxic injuries. This is in contrast with hypoxic injury during general and regional anesthesia, which accounted for only 2% of claims. While there were fewer claims related to MAC than for general anesthesia, approximately 41% of all claims related to either were for death or permanent brain damage (Figure 1). It is notable that some drugs commonly used in MAC are also utilized in moderate sedation—midazolam, fentanyl, and propofol—and can cause respiratory depression, particularly when combined.

The study emphasized a telling point: MAC, even when targeting moderate sedation, needs to be approached with the same care and attention as general and regional anesthesia.

**GETTING STARTED**

The process of administering procedural sedation begins with an evaluation of the patient, including medical history and physical examination. The examiner should be especially alert for indicators of

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**Table 1. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (2004)**

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Minimal Sedation (Anxiolysis)</th>
<th>Moderate Sedation/Analgesia (Conscious Sedation)</th>
<th>Deep Sedation/Analgesia</th>
<th>General Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Intervention often required</td>
</tr>
<tr>
<td>Spontaneous Ventilation</td>
<td>Unaffected</td>
<td>Adequate</td>
<td>May be inadequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td>Cardiovascular Function</td>
<td>Unaffected</td>
<td>Usually maintained</td>
<td>Usually maintained</td>
<td>May be impaired</td>
</tr>
</tbody>
</table>

*Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

**Sedation and Analgesia Techniques:**

Figure 1. Severity of injury in monitored anesthesia care (MAC), general, and regional anesthesia claims. The proportion of claims for death (14%) and permanent brain damage (7%) was reduced in regional anesthesia compared with MAC (33% death and 8% brain damage). In contrast, the severity of injury was similar between MAC claims and those associated with general anesthesia (27% death and 10% brain damage).

<table>
<thead>
<tr>
<th>% of claims in anesthesia group</th>
<th>MAC <em>(n=121)</em></th>
<th>General <em>(n=1,519)</em></th>
<th>Regional <em>(n=312)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/Permanent Brain Damage</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Permanent Disabling</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Temporary/ Nondisabling</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>


potentially increased risk for adverse outcomes from sedation, such as: significant cardiac or pulmonary disease; neurologic or seizure disorders; stridor, snoring, or sleep apnea; adverse reactions to sedation or anesthesia; current medications, drug and food allergies; and alcohol or drug abuse. The ASA’s physical status classification (P1-P5) is typically used to designate a patient’s overall health (Table 2). Those designated ASA I-III can be appropriate for routine sedation with approved drugs, while ASA IV and V patients may require reduced dosing and other special considerations, including use of an anesthesiologist or nurse anesthetist to administer the sedation.

During the procedure, sedated patients are given supplemental oxygen and must be carefully monitored. Typical monitoring includes the electrocardiogram, and blood pressure measurement, oxygenation with pulse oximetry, and, less frequently, capnography (although capnography is a routine monitor when anesthesia practitioners provide sedation).

Additionally, a patient’s level of consciousness should be assessed as soon as sedation is administered and throughout the procedure. A common assessment tool is the Modified Observer’s Assessment of Alertness and Sedation, which rates the patient’s responsiveness to various stimuli such as prodding, shaking, and calling of the patient’s name. Bispectral index (BIS) monitoring, a non-invasive measure of consciousness level, has been used, but its efficacy in procedural sedation has not yet been well established.

One of the significant challenges in procedural sedation is determining proper dosage and titration. As noted, individual patients respond differently to the same dose of the same sedative—up to a fivefold difference to a given agent. Clinicians must understand the pharmacokinetics and interactions of various agents. Many sedation drugs are used in combination, and the effects are typically synergistic not additive, requiring clinicians to understand the various properties of those combinations. For example, even a low dose of an opioid can substantially reduce the amount of benzodiazepine or propofol needed to maintain proper sedation during endoscopy.

Most regimens begin with an initial bolus of a sedative or opioid, followed by ongoing titration of one or more agents during the procedure. Practitioners delivering sedation must have knowledge of an individual agent’s onset and peak effect properties, being careful to distinguish between the two. Evaluating a patient’s sedation level before a drug’s peak effect is reached can lead to administering more sedative than necessary to maintain the

<table>
<thead>
<tr>
<th>Table 2. ASA Physical Status Classification System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P1</strong></td>
</tr>
<tr>
<td><strong>P2</strong></td>
</tr>
<tr>
<td><strong>P3</strong></td>
</tr>
<tr>
<td><strong>P4</strong></td>
</tr>
<tr>
<td><strong>P5</strong></td>
</tr>
</tbody>
</table>

desired level and result in adverse effects brought on by oversedation.

**AVAILABLE AGENTS**
The landscape of agents used in ambulatory sedation has changed significantly in recent years. Current staples include a benzodiazepine (most commonly midazolam and diazepam) with an opioid (often fentanyl or remifentanil), and propofol with or without a benzodiazepine and/or an opioid. Newer agents such as dexmedetomidine and fospropofol are attracting more attention. Ketamine, a rapid-acting agent usually employed for general anesthesia, has been used in low doses for moderate sedation and has been paired with low-dose propofol (Table 3).

Each agent and combination has particular advantages and drawbacks in the ambulatory setting: Opioids are primarily associated with analgesia, though they can be used as

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset of action (min)</th>
<th>Peak effect (min)</th>
<th>Duration of effect (min)</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Pharmacologic antagonist</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine (µg)</td>
<td>&lt;5</td>
<td>15</td>
<td>Unknown</td>
<td>1/kg</td>
<td>200</td>
<td>None</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>Diazepam (mg)</td>
<td>2-3</td>
<td>3-5</td>
<td>360</td>
<td>5-10</td>
<td>20</td>
<td>Flumazenil</td>
<td>Respiratory depression, chemical phlebitis</td>
</tr>
<tr>
<td>Diphenhydramine (mg)</td>
<td>2-3</td>
<td>60-90</td>
<td>&gt;240</td>
<td>25-50</td>
<td>400</td>
<td>None</td>
<td>Dizziness, prolonged sedation</td>
</tr>
<tr>
<td>Fentanyl (µg)</td>
<td>1-2</td>
<td>3-5</td>
<td>30-60</td>
<td>50-100</td>
<td>200</td>
<td>Naroxone</td>
<td>Respiratory depression, vomiting</td>
</tr>
<tr>
<td>Fospropofol (mg)</td>
<td>2-4</td>
<td>8-12</td>
<td>2-16</td>
<td>6.5/kg</td>
<td>577.5</td>
<td>None</td>
<td>Respiratory depression, hypoxemia, loss of purposeful responsiveness, hypotension</td>
</tr>
<tr>
<td>Ketamine (mg)</td>
<td>&lt;1</td>
<td>1</td>
<td>10-15</td>
<td>0.5/kg</td>
<td>Titrate to effect</td>
<td>None</td>
<td>Emergence reaction, apnea, laryngospasm</td>
</tr>
<tr>
<td>Meperidine (mg)</td>
<td>3-6</td>
<td>5-7</td>
<td>60-180</td>
<td>25-50</td>
<td>150</td>
<td>Naroxone</td>
<td>Respiratory depression, pruritus, vomiting, interaction with MAOI</td>
</tr>
<tr>
<td>Midazolam (mg)</td>
<td>1-2</td>
<td>3-4</td>
<td>15-80</td>
<td>1-2</td>
<td>6</td>
<td>Flumazenil</td>
<td>Respiratory depression, disinhibition</td>
</tr>
<tr>
<td>Promethazine (mg)</td>
<td>2-5</td>
<td>Unknown</td>
<td>&gt;120</td>
<td>12.5-25</td>
<td>100</td>
<td>None</td>
<td>Hypotension, respiratory depression, extrapyramidal effects</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>&lt;1</td>
<td>1-2</td>
<td>4-8</td>
<td>10-40</td>
<td>400</td>
<td>None</td>
<td>Respiratory depression, cardiovascular instability</td>
</tr>
</tbody>
</table>

*For healthy individual <60 years of age.
Fentanyl and meperidine are used as adjunctive analgesic therapy with propofol and benzodiazepines. Fentanyl is more potent than meperidine, and has a more rapid onset and shorter duration of action. It also has the potential to significantly depress respiratory function, particularly at higher doses. Remifentanil, a short-acting opioid, has been paired with a benzodiazepine in outpatient oral surgery. A recent study concluded that remifentanil with midazolam was safe and reliable during extraction of third molars. In another study, remifentanil produced significantly lower peak heart rate and systolic blood pressure levels as adjunct therapy in third molar extraction compared with meperidine. Remifentanil has also proven safe and effective in colonoscopy when combined with midazolam or propofol.

In addition to depressing respiratory function, other adverse effects of opioids are hypotension when combined with benzodiazepines, bradycardia, dysphoria, nausea, and vomiting. Opioids’ effects can be reversed by naloxone. Midazolam is a water-soluble agent that causes sedation, anxiolysis, and amnesia. Its peak effect is slower than that of diazepam, and it is the shortest-acting benzodiazepine available. Its typical half-life of 2 hours in healthy adults can be prolonged in patients aged >50 years.

A much more potent agent than diazepam, midazolam is typically paired with fentanyl or meperidine and has also been combined with propofol. A benzodiazepine with an opioid was the preferred regimen for three-fourths of surveyed endoscopists, and midazolam is considered the most widely used sedative for endoscopy.

In one nationwide survey, 85% of endoscopists reported using midazolam; fewer than 10% used diazepam. A recent meta-analysis found that midazolam was preferable to diazepam because of faster onset of action, shorter duration of action, and a lower proportion of patients with memory of the procedure. The study's pooled data show that a higher percentage of patients are satisfied with and would repeat sedation with midazolam vs. diazepam.

Overall, the meta-analysis reported an adequate or better level of sedation with midazolam in 94% of cases. Approximately 88% of physicians and 89% of patients were satisfied with the sedation experience, and 82% of patients would be willing to repeat the procedure with the same sedation.

One study of various elective endoscopic procedures using midazolam and meperidine found that unintended deep sedation occurred for 68% of patients, including 85% undergoing ERCP, 80% undergoing EUS, 60% undergoing EGD, and 45% undergoing colonoscopy. The synergistic effect of combining midazolam with an opioid reduces the amount of midazolam needed, but it also has the potential to cause significant respiratory depression and airway obstruction.

Common adverse effects of midazolam include atropine-resistant bradycardia, hypoxemia, hypotension, and, as noted, respiratory depression when paired with an opioid. The reversal agent for benzodiazepines is flumazenil. Propofol was approved by the FDA in 1989 for general anesthesia and is used widely in intensive care units for sedation of mechanically ventilated patients. It is an important sedative agent in ambulatory sedation. About one-fourth of endoscopists report using propofol for sedation for outpatient procedures, most commonly in collaboration with an anesthesiologist. Compared with benzodiazepines and opioids, the agent is associated with faster onset of action, more rapid recovery to full consciousness, minimal residual sedative effects, and higher patient satisfaction.

One study found a clear preference for propofol vs. midazolam and meperidine among surveyed gastroenterologists.

Table 4. Physician Ratings of Propofol vs. Midazolam and Meperidine

<table>
<thead>
<tr>
<th>Questionnaire item</th>
<th>Mean Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safer and smoother titration</td>
<td>3.4</td>
</tr>
<tr>
<td>More relaxed ambience</td>
<td>3.6</td>
</tr>
<tr>
<td>Procedure is faster</td>
<td>3.8</td>
</tr>
<tr>
<td>Better memory at discharge</td>
<td>3.8</td>
</tr>
<tr>
<td>More rapid discharge</td>
<td>4.0</td>
</tr>
<tr>
<td>Quicker to get started</td>
<td>4.0</td>
</tr>
<tr>
<td>Better patient tolerance</td>
<td>4.0</td>
</tr>
<tr>
<td>Better reputation in the community</td>
<td>4.0</td>
</tr>
<tr>
<td>More procedures in a fixed-bed recovery area</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Scores: 1 = very strongly disagree; 2 = somewhat disagree; 3 = very strongly agree; 4 = agree completely.
Propofol causes sedation, hypnosis, and anxiolysis.\textsuperscript{11} When used alone, propofol can be associated with coughing and pain-withdrawal movements that interrupt the procedure\textsuperscript{5} and can lead to administration of more propofol that pushes the patient into deep sedation. For this reason, propofol is typically used with fentanyl or meperidine to block the coughing and to add analgesia.

Propofol has also been combined with midazolam, though results have been inconsistent. One study concluded that oral midazolam combined with IV propofol reduced the amount of propofol needed and also reduced patient anxiety before ERCP;\textsuperscript{21} another showed that midazolam reduced the amount of propofol needed during EGD or ERCP but otherwise had no effect;\textsuperscript{22} and a third study reported that premedication with midazolam did not reduce the amount of propofol needed during EUS.\textsuperscript{23} Recently, a report noted that adding midazolam to propofol for colonoscopy did not result in more cognitive impairment vs. propofol alone but did improve the ease of colonoscopy without increasing the rate of complications or recovery times.\textsuperscript{24}

Many favor what is called “balanced propofol sedation.” This regimen begins with low doses of midazolam and an opioid, then propofol is titrated to establish moderate sedation.\textsuperscript{25,26} The advantages of this approach include maintaining a reversible agent (for midazolam and the opioid) and simplifying the administration of propofol, which is given less often and in smaller doses, lessening the risk of deep sedation. In a study of 100 cases using this technique, deep sedation was recorded in only 2% of assessments and never for longer than 2 minutes.\textsuperscript{26}

A major issue with propofol has been how it is formulated. Propofol cannot be easily dissolved in water, and thus miscibility can be achieved only in lipophilic substances. The current formulation includes propofol in a combination of soybean oil, glycerol, and egg lecithin.\textsuperscript{27} The lipid component can support growth of microorganisms. In the United States, disodium edetate (EDTA) or metabisulfite is added to retard such growth.

Propofol’s formulation can contribute to unwanted effects such as pain on injection, allergic reactions, microbial growth, alteration of a patient’s lipid profile, and what has become known as “propofol infusion syndrome,” which is characterized by cardiac failure, acidosis,
and rhabdomyolysis. A recent spot-check survey of anesthesia professionals found that pain on injection was rated by 79% of respondents as the biggest of problems presented by propofol.28

The Centers for Disease Control and Prevention (CDC) first documented propofol infection risk in seven hospitals between 1990 and 1999, eliciting calls for strict aseptic techniques when handling the agent.29 With awareness of the risk and the addition of ethylenediaminetraacetic acid (EDTA) as an antimicrobial, this risk was presumably decreased. However, in June 2007, the FDA issued an alert noting “several clusters of patients who have experienced chills, fever, and body aches shortly after receiving propofol.” The agency emphasized compliance with strict handling protocols.30

As with many sedative agents, propofol causes respiratory depression, which is exacerbated by opioids. Propofol has also been associated with hypotension and has been found to cause hypertriglyceridemia if given in sufficient quantities (usually over a prolonged period in the ICU).11,27

Propofol’s kinetics include rapid onset and offset (Figures 2 and 3). Rapid onset can be an advantage allowing for a more rapid establishment of the sedated state. It can also be a disadvantage because patients can enter quickly into deeper-than-intended sedation if the clinician administering the drug is not experienced and well-trained. That risk led the US Food and Drug Administration to include labeling that restricts use of propofol in sedation to anesthesiology professionals.27 Rapid offset leads to shorter recovery times, and propofol has a favorable profile regarding nausea and vomiting.31,32

Propofol has no reversal agent; this is often considered a disadvantage of propofol. Fospropofol, a prodrug of propofol, was approved for use in MAC in December 2008. The body’s alkaline phosphatases completely and rapidly metabolize fospropofol into propofol, formaldehyde, and phosphate. Like propofol, fospropofol causes sedation, hypnosis, and anxioly-
tion in intubated and mechanically ventilated ICU patients. In October 2008, the FDA added approval for use in non-intubated patients prior to and/or during surgical and other procedures.

The approval for the new indication was based on a Phase 3 clinical trial by Candrilli and colleagues. The study looked at 326 patients undergoing various elective procedures that called for MAC. Both the placebo arm and dexmedetomidine arms (at loading doses of 0.5 or 1 mcg/kg) received midazolam to titrate to adequate sedation, and fentanyl was given when needed for pain. The placebo arm roughly approximated a typical midazolam-fentanyl combination sedation approach.

The dexmedetomidine arms used significantly less midazolam and fentanyl to maintain sedation than the midazolam-fentanyl arm. The midazolam-fentanyl group saw 12.7% of patients experience respiratory depression, defined as O2 saturation <90% and a respiratory rate <8. The two dexmedetomidine arms had respiratory depression rates of 3.7% and 2.3% for the lower and higher doses, respectively.

Other advantages for dexmedetomidine vs. midazolam-fentanyl in the study included: significantly fewer patients required postoperative analgesics; anxiety scores were significantly lower; and patient satisfaction measured by the Iowa Satisfaction with Anesthesia Scale was significantly higher.

Other studies have found dexmedetomidine safe and effective for procedures in plastic surgery, ophthalmology, orthopedics, and vascular surgery as well as for upper gastroscopy and breast biopsies.

It has also been studied in dental procedures. Ustun and colleagues compared dexmedetomidine with midazolam during sedation for third molar surgery. They found dexmedetomidine a “reliable and safe method, with additional analgesic effect providing a satisfactory sedation level without any serious side effects during impacted third molar surgery.”

Adverse effects with an incidence of >2% include hypotension, bradycardia, and dry mouth, and were found by one study to be significant. In that study, Jalowiecki et al halted their efforts to evaluate dexmedetomidine in colonoscopy because of adverse events. The study was designed to compare dexmedetomidine alone to midazolam-meperidine and to on-demand fentanyl. The dexmedetomidine group experienced prolonged recovery times and profound hypotension and bradycardia. Intensive medical interventions were needed in 3 of 19 patients receiving dexmedetomidine.

Ketamine is used most often in general anesthesia and has been combined with propofol in various settings. The two agents are combined in one syringe or given in separate syringes. The concept is to pair the two agents at doses lower than those required if using either drug alone, and therefore minimize the adverse effects associated with each.

Ketamine and propofol have been studied in pediatrics, cosmetic surgery, emergency departments (EDs), and in hard-to-sedate cases, with mixed results. For example, Willman and Andolfatto found that ketamine-propofol was safe and effective for painful ED procedures, elicited few adverse events, and produced rapid recovery times and highly satisfied patients and staff. On the other hand, Slavik and Zed declared that “combination propofol and ketamine has not demonstrated superior clinical efficacy compared with propofol alone for procedural sedation and analgesia.”

**PROPOFOL ADMINISTRATION**

The administration of propofol outside the operating room has generated considerable controversy. The FDA mandated product labeling on both propofol and fospropofol that the drugs “should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.”

The American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy issued a joint statement in 2004 disagreeing with the FDA’s recommendation and offering their own:

- There are data to support the use of propofol by adequately trained non-anesthesiologists. Large case series indicate that with adequate training, physician-supervised nurse administration of propofol can be done safely and effectively.
- The routine assistance of an anesthesiologist/anesthetist for average-risk patients undergoing standard upper and lower endoscopic procedures is not warranted.

Concerned that propofol’s rapid action could move patients quickly through moderate sedation, deep sedation, and general anesthesia, and noting that the drug has no reversal agent, the ASA and the American Association of Nurse Anesthetists then issued a joint statement declaring that failure to adhere to the packaging recommendations “could put patients at increased risk of significant injury or death.”

Advocates for only anesthesia-trained clinicians using propofol express concerns that administration by other specialists may lead to avoidable adverse events. Deep sedation using propofol is a technically complex task, they argue, with a substantial learning curve and is beyond the expertise of practitioners without formal anesthesia training.

Despite such arguments, it is generally conceded that use of propofol by non-anesthesiologists is commonplace. A recent study in *Annals of Emergency Medicine* noted 28 published studies showing the safety and efficacy of...
propofol use in nearly 4,000 ED patients. Authors argued that “a residency-trained emergency physician possesses the ideal skill set for deep sedation” and concluded that “deep sedation using propofol is rapidly evolving into an essential emergency physician skill.”

A more controversial issue is nurse-administered propofol sedation (NAPS) for various endoscopic procedures, most commonly colonoscopy. A number of studies have investigated the safety and efficacy of propofol, including one that looked at more than 9,000 endoscopic cases in an Oregon ambulatory surgery center. That study reported that only 7 patients suffered respiratory compromise, 3 experienced prolonged apnea accompanied by hypoxemia due to oversedation, and none required endotracheal intubation, laryngeal mask airway or rescue by an anesthesiologist.

On the other hand, another study involved more complex procedures such as ERCPs and a significant number of ASA class III and IV patients. Out of more than 9,500 cases where propofol was delivered by a non-anesthesiologist physician, there were 135 adverse events, including 117 from oversedation, 4 deaths (3 from oversedation), 40 patients who needed assisted ventilation, 9 who needed endotracheal intubation, and 28 who needed monitoring in the ICU.

Most recently, Rex and colleagues reported on 646,000 cases of endoscopist-directed propofol (EDP) sedation worldwide, including 223,000 in published studies. Of those EDP cases, investigators reported 11 endotracheal intubations, no permanent neurologic injuries, and 4 deaths. They concluded that the safety record of EDP was comparable to that of published data on general anesthesia by anesthesiologists and better than that of endoscopist-delivered benzodiazepines and opioids.

The controversy over who is qualified to administer propofol is far from settled and promises to be a topic of great interest and debate.

**ON THE HORIZON**

Because propofol is effective in patients yet problematic in its delivery, researchers are trying to develop improved formulations, including those with new lipid-type approaches. Other efforts have focused on cyclodextrin-based formulations that attempt to make propofol water soluble and thus minimize the injection pain associated with lipid delivery systems.

Unfortunately, in at least one lab the cyclodextrin-based formulation actually increased injection pain. Other approaches have included microemulsion formulation, which in one study produced efficacy and safety results similar to a lipid emulsion, and micellar solution, or nanotechnology, which aims to manifest propofol’s natural antimicrobial activity.

Delivering propofol more efficiently is also the subject of emerging solutions. The most common device used in the United States to deliver propofol is a calculator pump. The user sets a target concentration based on knowledge of the drug’s therapeutic window. The TCI computer, using the drug’s pharmacokinetic model, then calculates the proper dosage to maintain that target concentration, and the pump delivers a time-varying infusion. The user can adjust the target concentration based on patient response. The TCI pump displays the patient’s predicted drug concentration in addition to the infusion rate.

Studies have evaluated TCI for endoscopy and found the technique safe and effective for propofol alone and propofol plus midazolam. TCI systems are not approved for use in the United States but are used regularly in other parts of the world. Advocates hope they will be available in the United States within a few years.

A similar technologic approach is computer-assisted personalized sedation (CAPS), which uses computerization to personalize drug delivery based on an individual patient’s physiology.

In May 2009, an FDA advisory committee recommended approval of a CAPS device named Sedasys® (Sedasys® is a trademark of Ethicon Endo-Surgery). The device integrates delivery of propofol and oxygen with patient monitoring of pulse oximetry, capnometry, ECG, noninvasive blood pressure, and patient responsiveness. It can automatically detect oxygen saturation and apnea and aims to regulate propofol infusion to avoid oversedation. Sedasys® is designed for physician/nurse teams.

A feasibility study published in 2008 reported on the use of Sedasys® with colonoscopy and EGD procedures. Desired sedation was achieved with about one-third of propofol dosages used in the NAPS trial. Postprocedure recovery was shortened to <30 seconds, leading to high satisfaction from both subjects and clinicians.

Results from a larger study that compared Sedasys® with a regimen of midazolam and an opioid were presented to the FDA. That study found that patients who received sedation from Sedasys® experienced fewer and less significant episodes of oxygen desaturation.

A new development that could impact computerized propofol delivery is the successful measurement of propofol in expired gas. This method uses mass spectrometry to measure exhaled propofol concentration in parts per billion in real
time. At least two studies have compared plasma and exhaled propofol concentrations and found that the expired gas measurement could be successfully used for real-time propofol monitoring.6,4

One innovative technologic approach allows patient-controlled sedation (PCS). A recent study compared PCS with propofol and remifentanil to PCS with midazolam and fentanyl for colonoscopy. Investigators found that the propofol/remifentanil group yielded better results, including shorter recovery time.40

An older study looked at PCS with propofol and alfentanil vs. traditionally delivered diazepam and meperidine.66 Patients in the PCS group recovered significantly faster (median 5 minutes vs. 35 minutes; P < .0001) but reported significantly higher pain scores.

PCS has also been studied in oral surgeries and been found effective with propofol,67 midazolam,12 and midazolam and remifentanil.13

CONCLUSION
Sedation and analgesia techniques make up a fast-moving field with new agents and new combinations of existing agents aimed at making patients safer and more comfortable during diagnostic and therapeutic procedures. New developments—both pharmacologic and technologic—are also targeted at giving clinicians more choice of regimens and easier and more effective use of medications.

Patients are increasingly expecting safe, pain- and anxiety-free outpatient procedures with little recovery time, even for relatively complicated procedures. To successfully meet that demand in the future will require new agents and combinations of agents, new delivery mechanisms, and new sedation strategies. The future promises to hold more innovations that will provide clinicians with added tools and tactics to satisfy patients’ high expectations.

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SEDATION AND ANALGESIA TECHNIQUES:

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54. Wehrmann T, Riphaus A. Sedation with propofol for interventional endoscopic proce-
66. Bright E, Roseveare C, Dagleish D, et al. Patient-controlled sedation for colonoscopy: a randomized trial comparing patient-controlled administration of propofol and alfentanil with physician-administered midazolam and pethi-
1. What is the percentage of endoscopic diagnostic and therapeutic procedures in the United States performed with sedation rather than general anesthesia?
   a. 50%
   b. 75%
   c. 85%
   d. 98%

2. The level of sedation that includes a state in which a patient is not easily aroused but responds purposefully to repeated or painful stimulation is
   a. Minimal
   b. Moderate
   c. Deep
   d. General anesthesia

3. Which of the following indicates increased risk of adverse outcomes from sedation?
   a. Diabetes
   b. Family history of sedation problems
   c. Snoring
   d. Mild dyslipidemia

4. Three-quarters of surveyed endoscopists favored which sedation regimen?
   a. Benzodiazepine with an opioid
   b. Benzodiazepine alone
   c. Propofol alone
   d. Dexmedetomidine with a benzodiazepine

5. Which of the following is a common effect of midzolam?
   a. Coughing
   b. Anterograde amnesia
   c. Dry mouth
   d. Bradycardia

6. Coughing and pain-withdrawal movements that impede a procedure can be associated with which agent(s)?
   a. Benzodiazepine with opioid
   b. Propofol with opioid
   c. Propofol alone
   d. Dexmedetomidine alone

7. Brief but intense perineal paresthesias can result from the use of which agent(s)?
   a. Fospropofol alone
   b. Midazolam with fentanyl
   c. Fentanyl alone
   d. Propofol with any opioid

8. In the Phase 3 study by Candiotti et al, which adverse effect was significantly more present in the midazolam-fentanyl group than in the dexmedetomidine arms?
   a. Increased anxiety
   b. Respiratory depression
   c. Bradycardia
   d. Hypotension

9. Which of the following drugs have/has no reversal agents?
   a. Meperidine and midazolam
   b. Propofol and fospropofol
   c. Diazepam
   d. Fentanyl

10. What is the one reason researchers are investigating micellar solution (nanotechnology) for propofol delivery?
    a. To increase the speed of onset
    b. To reduce injection pain
    c. To release propofol’s natural antimicrobial activity
    d. To allow non-anesthesiologists to administer propofol more safely
PROGRAM EVALUATION AND ANSWER SHEET

Please read the monograph and take the test. Fill in the answer sheet and submit it to BUSM CME before November 29, 2010. CME credit will be awarded if a score of 70% or better is achieved. To receive CE credit, nurses must pass the post-test with a score of 80% or better. Submit the answer sheet via mail or fax to: Boston University School of Medicine, Continuing Medical Education, E.SAMBAHAY09, 72 East Concord St., A305, Boston, MA 02118. Fax 617-638-4905. Your certificate will be mailed to you in 4-6 weeks. To participate online and receive your certificate instantly, go to www.bucmetest.com. Enter E.SAMBAHAY09 in the Test Code Search Field. For questions, please contact BUSM CME at 617-638-4605.

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The amount of time I spent on this activity was ___________ (max of 1 hour).

Exam Answer Form  Darken the circle with the correct answer to each question in the CME/CE activity.

1. A  B  C  D
2. A  B  C  D
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8. A  B  C  D
9. A  B  C  D
10. A  B  C  D

Program Evaluation

1. How would you rate this activity overall? (5 = excellent, 1 = poor; please circle one)
   5  4  3  2  1
2. Do you feel each of the learning objectives listed on page 2 was met?
   Objective 1  Yes  Partially  No  N/A
   Objective 2  Yes  Partially  No  N/A
   Objective 3  Yes  Partially  No  N/A
   Objective 4  Yes  Partially  No  N/A
   Objective 5  Yes  Partially  No  N/A
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   4a. Timely, up to date?  5  4  3  2  1
   4b. Relevant to your practice?  5  4  3  2  1
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