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AGA Institute Review of Endoscopic Sedation

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Sedation and analgesia are considered by many gastroenterologists to be an integral component of the endoscopic examination. For example, more than 98% of endoscopists in the United States routinely administer sedation during upper and lower endoscopies.¹ Sedation is intended primarily to reduce a patient's anxiety and discomfort, consequently improving their tolerability and satisfaction for the procedure. Endoscopic sedation also minimizes a patient's risk of physical injury during an examination and provides the endoscopist with an ideal environment for a thorough examination. Despite the benefits of sedation, its use remains problematic. Sedation delays patient recovery and discharge, adds to the overall cost of an endoscopic procedure, and increases the risk of cardiopulmonary complications. Notwithstanding these considerations, the use of sedation during endoscopy continues to increase throughout the world.¹⁻⁴

Sedation may be defined as a drug-induced depression in the level of consciousness. Four stages of sedation have been described, ranging from minimal (anxiolysis) to moderate (conscious sedation), deep, and general anesthesia.⁵ Although many patients tolerate endoscopy with moderate sedation, some patients will require deep sedation. Knowledge of the pharmacologic profiles of sedation agents is necessary to maximize the likelihood that the desired level of sedation is targeted accurately. Nonetheless, individuals differ in their response to sedation and a patient may become more deeply sedated than the level that was intended. Therefore, practitioners should possess the skills necessary to resuscitate or rescue a patient whose level of sedation is deeper than that planned.

This review is designed to standardize the practice of endoscopic sedation within the United States. Whenever possible, the statements and recommendations were developed systematically from an evidence-based analysis of the literature. There are many areas in which evidence from randomized, controlled studies is absent, and conclusions are drawn from case series, retrospective database studies, and the opinion of experts in anesthesia and endoscopy. It is hoped that practitioners will use this

document to develop a structured sedation protocol suited to the needs of their patients and practice. Implementation of an evidence-based sedation protocol has been shown to improve the quality of practice and reduce the incidence of sedation-related adverse events.^{6,7}

General Guidelines

Preprocedure Assessment

An evaluation of the patient should precede the administration of intravenous sedation. This assessment is designed to identify those aspects of a patient's medical history and physical examination that could adversely affect the outcome of endoscopic sedation. Essential elements of the medical history include the following: (1) significant cardiac or pulmonary disease; (2) neurologic or seizure disorder; (3) stridor, snoring, or sleep apnea; (4) adverse reaction to sedation or anesthesia; (5) current medications, drug and food allergies; (6) alcohol or drug abuse; and (7) time of last oral intake. In addition, a patient's overall comorbid disease risk should be classified according to the American Society for Anesthesiology (ASA) physical status classification (Table 1).⁸ ASA class I-III patients are appropriate candidates for administration of sedation by an endoscopist. The assistance of an anesthesia specialist should be considered for ASA classes IV and V patients requiring sedation, emergency endoscopic procedures, complex endoscopic procedures such as endoscopic retrograde cholangiopancreatography and endoscopic ultrasound, and patients with a history of (1) adverse reaction to sedation, (2) alcohol or substance abuse, or (3) inadequate response to moderate sedation.

Abbreviations used in this paper: ACLS, advanced cardiac life support; ASA, American Society for Anesthesiology; BIS, bispectral index; EGD, esophagogastroduodenoscopy; FDA, food and drug administration; GABA, γ -aminobutyric acid; GD-P, gastroenterologist-directed propofol; GI, gastrointestinal; NAPS, nurse-administered propofol sedation; TCI, target-controlled infusion.

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Table 1. ASA Classification

Class	Description
I	The patient is normal and healthy
II	The patient has mild systemic disease that does not limit their activities (eg, controlled hypertension or controlled diabetes without systemic sequelae)
III	The patient has moderate or severe systemic disease, which does limit their activities (eg, stable angina or diabetes with systemic sequelae)
IV	The patient has severe systemic disease that is a constant potential threat to life (eg, severe congestive heart failure, end-stage renal failure)
V	The patient is morbid and is at substantial risk of death within 24 hours (with or without a procedure)
E	Emergency status: in addition to indicating underlying ASA status (1–5), any patient undergoing an emergency procedure is indicated by the suffix "E"

The literature contains a variety of recommendations for fasting before procedural sedation. This reflects the fact that there are no studies showing a direct relationship between fasting time and the risk of pulmonary aspiration. Consequently, no practice standard for preprocedural fasting has been accepted universally. The ASA guidelines indicate that patients should fast a minimum of 2 hours for clear liquids and 6 hours for light meal before sedation.⁹ However, the American College of Emergency Physicians concluded "recent food intake is not a contraindication for administering procedural sedation and analgesia, but should be considered in choosing the timing and target level of sedation."¹⁰ There is inadequate evidence to permit the development of absolute requirements for preprocedural fasting, and the clinician should be guided by the parameters provided by various professional societies.

A focused physical examination should include the following: (1) vital signs and weight, (2) auscultation of heart and lungs, (3) baseline level of consciousness, and (4) assessment of airway. The airway evaluation is designed to identify patients with anatomy that may make positive-pressure ventilation more difficult. This includes patients with obesity, short thick neck, cervical spine disease, decreased hyoid-mental distance, and structural abnormalities of the mouth, jaw, and oral cavity. Examination of the oral cavity also is useful for identifying individuals with anatomy that is associated with more difficult intubation (Figure 1).^{11,12}

All medical facilities performing endoscopy should have established guidelines that specify when pregnancy testing is indicated.¹³ Within some institutions, it is standard policy to routinely query all female patients of childbearing age regarding the possibility of pregnancy. Depending on local policy, a "yes" or "no" answer may suffice, or a pre-sedation pregnancy test may be required. Pregnant patients should be advised of the risks of endoscopy and sedation, and elective procedures should be deferred whenever possible. The selection of pharmaco-

logic agents in a pregnant patient is complex and takes into account the Food and Drug Administration (FDA) pregnancy classification, the anticipated duration of the procedure, and the potential for adverse physiologic events including hypotension and hypoxemia. Benzodiazepines are the only category D drug used in endoscopy and should be avoided if possible, especially during the first trimester.¹⁴

Documentation of the preprocedural assessment should be confirmed before initiating sedation. If this assessment was performed in advance of the scheduled examination, a brief review and re-confirmation is recommended just before initiating sedation. The patient's name and procedure to be performed should be confirmed during a "time-out" before sedation is initiated.¹⁵

Laboratory testing is not indicated routinely for patients undergoing endoscopic sedation. In select cases, however, testing may be appropriate before a procedure if there is reason to believe that the result will alter the conduct of sedation.

Recovery and Discharge

After the completion of endoscopy, patients receiving intravenous sedation require observation and monitoring. The individual assigned to this task should possess training and experience comparable with nurses assisting with endoscopic procedures. Level of conscious-

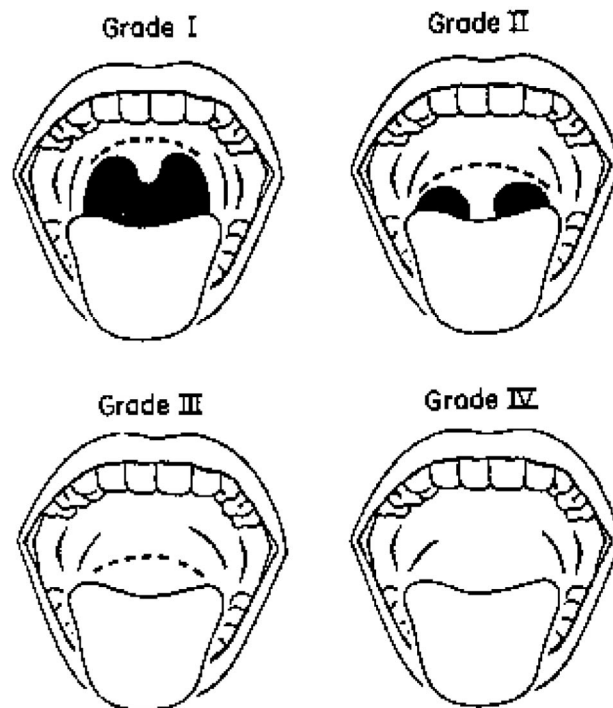


Figure 1. Mallampati score used to predict difficult intubation. This system emphasizes the importance of the base of the tongue in predicting difficulty with laryngoscopy. If the faucial pillars and uvula cannot be adequately visualized on maximal mouth opening (Mallampati III and IV), visualization of the glottis is likely to be more difficult.

Table 2. Aldrete Scoring Systems

Respiration	
Able to take deep breath and cough =	2
Dyspnea/shallow breathing =	1
Apnea =	0
O ₂ saturation	
S _a O ₂ >95% on room air =	2
S _a O ₂ = 90%–95% on room air =	1
S _a O ₂ <90% even with supplemental O ₂ =	0
Consciousness	
Fully awake =	2
Arousable on calling =	1
Not responding =	0
Circulation	
BP ± 20 mm Hg baseline =	2
BP ± 20–50 mm Hg baseline =	1
BP ± 50 mm Hg baseline =	0
Activity	
Able to move 4 extremities =	2
Able to move 2 extremities =	1
Able to move 0 extremities =	0

NOTE. Monitoring may be discontinued and patient discharged to home or appropriate unit when Aldrete score is 9 or greater.

ness, hemodynamic parameters, oxygenation, and pain/discomfort should be evaluated at regular intervals and recorded until these measures all have returned to baseline. Patients receiving naloxone and/or flumazenil require more extended monitoring (up to 2 hours). The duration of effect for these agents is shorter than that of the opioids and benzodiazepines; consequently, there is a risk of re-sedation and cardiopulmonary instability as the effect of the antagonist wears off.

Standardized discharge criteria should be used to assess recovery from sedation. This practice is designed to facilitate safe and efficient discharge.¹⁶ Several recovery scales have been developed, most using similar criteria to assess eligibility for discharge. One such example is the Aldrete scoring system, which evaluates 5 physiologic parameters: activity, respiration, oxygen saturation, blood pressure, consciousness, and activity (Table 2).¹⁶ In addition to a physiologic assessment, suitability for discharge includes an ability to dress and walk independently. Patients need not be assessed for their ability to tolerate fluids or solids before discharge home. All patients should receive verbal and written instructions outlining diet, activity, medication, and follow-up evaluation. A contact person and telephone number with availability 24 hours/day should be provided to all patients in the event of a complication related to the endoscopic procedure. On discharge, a responsible individual should accompany the patient home.

Documentation

Documentation is an essential element of patient care throughout all phases of the endoscopic procedure. This includes the preprocedure assessment, informed consent, intraprocedural monitoring, recovery, and dis-

charge. The chart should contain a time-based record of all drugs administered including name and dosage, the type and quantity of intravenous fluids, and whether oxygen was administered (and flow rate). A periodic assessment of the patient's level of sedation (using a sedation scale) and level of pain (using a pain scale) also should be indicated.

Documentation is accomplished most efficiently using a standardized form that conforms to all institutional policies and practice standards pertaining to procedural sedation. The use of a structured document prompts the physician to complete all aspects of the evaluation. The implementation and use of a standardized form has been shown to improve compliance with documentation and reduce the frequency of sedation-related adverse events.⁷

Quality Improvement

A system for assessing outcome measures and complications related to sedation should be established at each facility. At the current time, no set of clinically important quality indicators to assess sedation has been accepted universally. It is somewhat easier to define sedation-related adverse events: hypoxemia requiring airway intervention, hypotension or bradycardia requiring pharmacologic intervention, pulmonary aspiration, laryngospasm, unanticipated use of reversal agents, and unanticipated hospitalization.

All adverse events as well as near-misses should be reported and analyzed. Such a process of self-examination is designed to identify and remedy areas of vulnerability. The ultimate goal of a quality-assurance program is an improvement in practice safety.¹⁷

Summary Statements and Recommendations

1. A preprocedure evaluation of the patient should be performed before endoscopy to identify pertinent history and physical findings that could affect the outcome of sedation adversely. The findings of this assessment should be documented before initiating sedation. The implementation of a structured form designed specifically for procedural sedation improves compliance with this process.
2. The use of an anesthesia professional should be strongly considered for ASA physical status IV and V patients. Other possible indications for an anesthesia specialist include patients with a history of alcohol or substance abuse, pregnancy, morbid obesity, neurologic or neuromuscular disorders, and patients who are uncooperative or delirious. Endoscopic procedures that may require an anesthesia specialist include endoscopic retrograde cholangiopancreatography, stent placement in the upper gastrointestinal tract, endoscopic ultrasound, and complex therapeutic procedures (eg, endoscopic submucosal dissection, plication of the cardioesophageal junction, esophagogastroduodenoscopy [EGD] with drainage of a pseudocyst).

Table 3. Pharmacologic Profile of Drugs Used for Endoscopic Sedation

Drug	Onset of action (min)	Peak effect (min)	Duration of effect (min)	Dosing for endoscopic sedation ^a		FDA pregnancy category	Pharmacologic antagonist	Significant adverse effects
				Initial dose	Maximum dose			
Dexmedetomidine (μg)	<5	15	Unknown	1/kg	200	C	None	Hypotension, bradycardia
Diazepam (mg)	2–3	3–5	360	5–10	20	D	Flumazenil	Respiratory depression, chemical phlebitis
Diphenhydramine (mg)	2–3	60–90	>240	25–50	400	C/B 3rd trimester	None	Dizziness, prolonged sedation
Droperidol (mg)	3–10	30	120–240	1.25–2.5	10	C	None	QT prolongation, ventricular arrhythmia, extrapyramidal effects
Fentanyl (μg)	1–2	3–5	30–60	50–100	200	C	Naloxone	Respiratory depression, vomiting
Flumazenil (mg)	1–2	3	60	0.1–0.3	>5	C		Agitation, withdrawal symptoms
Ketamine (mg)	<1	1	10–15	0.5/kg	Titrate to effect	B	None	Emergence reaction, apnea, laryngospasm
Meperidine (mg)	3–6	5–7	60–180	25–50	150	C	Naloxone	Respiratory depression, pruritus, vomiting, interaction with MAOI
Midazolam (mg)	1–2	3–4	15–80	1–2	6	D	Flumazenil	Respiratory depression, disinhibition
Naloxone (mg)	1–2	5	30–45	0.2–0.4	>2	B		Narcotic withdrawal
Nitrous oxide	2–3	Dose-dependent	15–30	Titrate to effect	Titrate to effect	?	None	Respiratory depression, headache
Promethazine (mg)	2–5	Unknown	>120	12.5–25	100	C	None	Hypotension, respiratory depression, extrapyramidal effects
Propofol (mg)	<1	1–2	4–8	10–40	400	B	None	Respiratory depression, cardiovascular instability

^aFor healthy individual <60 yrs of age.

Pharmacology of Sedation

The goal of endoscopic sedation is to maximize patient comfort while minimizing the risk of drug-related side effects. Achieving optimal sedation requires careful consideration of patient and procedure-related variables. Patient factors include age, health status, concurrent medications, preprocedural anxiety, and pain tolerance. The procedural variables include the degree of invasiveness, level of procedure-related discomfort, and the duration of examination. The drugs most widely used for endoscopic sedation are the benzodiazepines and opioids. Recently, there has been growing interest in the use of other agents with unique pharmacologic properties designed to enhance sedation and analgesia, reduce undesirable side effects, or both. The practitioner administering sedation should possess a thorough understanding of the pharmacologic profile of all drugs used within their facility. For each drug, this includes knowledge of its pharmacokinetic parameters (time of onset, peak response, and duration of effect), pharmacodynamic profile (interindividual variations in responsiveness to a drug), adverse effects, and drug–drug interactions.¹⁸ Table 3 summarizes the pharmacologic profile of the drugs used most often for endoscopic sedation.^{19,20}

Opioids

The principle effects of the opioid class of drugs, including morphine, meperidine, and fentanyl, are analgesia and sedation. Opioids exert their pharmacologic effects by binding to specific opioid receptors that are present throughout the central nervous system and peripheral tissues. The differences in chemical structure between these medications account for differences in their pharmacokinetic parameters and analgesic effect.

Meperidine. The induction dose of meperidine for conscious sedation is 25–50 mg administered slowly over 1–2 minutes. Additional doses of 25 mg may be administered every 2–5 minutes until adequate sedation is achieved. Its onset of action is 3–6 minutes, while its duration of effect ranges from 1 to 3 hours. N-demethylation of meperidine by the liver creates normeperidine, an active metabolite with potent central excitatory toxicity. The half-life of meperidine may be prolonged significantly with renal insufficiency, increasing the potential for neurotoxicity.²¹

In clinical practice, opioids usually are combined with a benzodiazepine for endoscopic sedation. Donnelly et al²² compared meperidine (50 mg) and diazepam (90 μg/kg) with alfentanil (250 μg) and midazolam (50 μg/

kg) in 60 patients undergoing EGD. The group receiving alfentanil and midazolam had faster induction time and fewer adverse movements during endoscopy. Deeper sedation scores were recorded in the alfentanil/midazolam group 30 minutes after endoscopy, but not after 60 minutes. There were no serious adverse events in either treatment group.

The major adverse effects associated with meperidine are respiratory depression and, to a lesser extent, cardiovascular instability. The concomitant use of a barbiturate or benzodiazepine with an opioid has a synergistic effect on the risk of respiratory depression.²³ Opioid-induced nausea and vomiting, resulting from stimulation of the medullary chemoreceptor trigger zone, is not a dose-dependent reaction. A neurotoxic reaction with irritability, tremor, myoclonus, and seizures caused by the accumulation of normeperidine has been reported in patients with renal failure.²⁴ Life-threatening complications can occur as a result of the drug interaction between meperidine and a monoamine oxidase inhibitor. Manifestations of this excitatory interaction include agitation, headache, hemodynamic instability, rigidity, seizures, and death. Unlike meperidine, fentanyl and the other opioids have not been implicated in this serious interaction with monoamine oxidase inhibitors.²⁵

Fentanyl. Fentanyl, a synthetic opioid narcotic, is highly lipid soluble and rapidly reaches opioid receptors. After an intravenous dose of 100 μg , its onset of action is 1–2 minutes and its duration of effect is 30–60 minutes. The initial dose of fentanyl is usually 50–100 μg . Supplemental doses of 25 μg each may be administered every 2–5 minutes until adequate sedation is achieved. A dose reduction of 50% or more is indicated in the elderly.

Stephens et al²⁶ compared the effect of fentanyl and diazepam in 200 consecutive outpatients undergoing EGD. Patients receiving fentanyl tolerated endoscopy better than those receiving diazepam, and recovery time was shorter in the fentanyl group. In contrast, others²⁷ have reported improved patient tolerance for EGD with diazepam compared with fentanyl.

The major adverse effect associated with fentanyl administration is respiratory depression, which may persist longer than the analgesic effect. In large doses, fentanyl may induce chest-wall rigidity, resulting from centrally mediated, generalized hypertonicity of skeletal muscle. In such cases, assisted ventilation of the patient may become difficult. Fentanyl has relatively little effect on the cardiovascular system, although a small reduction in arterial blood pressure and heart rate may occur in response to vagal stimulation. The incidence of nausea and vomiting with fentanyl is similar to other opioids.

Naloxone. Naloxone hydrochloride is an opioid antagonist that is related structurally to oxymorphone. It antagonizes all of the central nervous system effects of the opioids, including ventilatory depression, excessive sedation, and analgesia. Naloxone possesses no intrinsic

agonist activity, and is ineffective for reversing the effects of nonopioid drugs such as benzodiazepines and barbiturates.

The onset of action after intravenous naloxone is 1–2 minutes, and its half-life is 30–45 minutes. The administration of additional doses of naloxone may be required in patients receiving narcotics with a longer half-life. Patients receiving naloxone should be monitored for an extended period of time (up to 2 hours).

It is recommended that patients receive a dose of .2–.4 mg (.5–1.0 $\mu\text{g}/\text{kg}$) intravenously every 2–3 minutes until the desired response is attained. Supplemental doses may be necessary after 20–30 minutes.

There are no prospective trials evaluating the use of naloxone for rescue of patients experiencing an opioid-induced adverse effect during endoscopy. Naloxone has been shown to be safe when used for the treatment of patients with an opiate overdose. Doses as high as 24 mg have been administered without any significant side effect.²⁸ Caution should be exercised in administering naloxone to patients with a history of chronic opioid or drug use because of the risk of inducing acute narcotic withdrawal.

Benzodiazepines

The pharmacologic effects of benzodiazepines include anxiolysis, sedation, amnesia, anticonvulsant, muscle relaxation, and anesthesia. The amnestic effect may persist after sedation has worn off. Benzodiazepines enhance activity of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) by binding to the GABA_A receptor subtype, located mostly on the postsynaptic nerve membranes within the cerebral cortex. The pharmacologic properties of various benzodiazepines are believed to result from individual differences in their affinity and binding to distinct GABA_A subunits.²⁹

Diazepam. Diazepam, developed in 1959, is an intravenous and orally active benzodiazepine. The initial induction dose for endoscopic procedures is 5–10 mg intravenously over 1 minute. If required, additional doses may be administered at 5-minute intervals. Dose reduction is required in debilitated or elderly patients. In general, 10 mg is sufficient for most endoscopic procedures, although up to 20 mg may be necessary if a narcotic is not being co-administered. Diazepam undergoes hepatic conversion to an active metabolite with slow metabolic clearance, accounting for its relatively long duration of effect.

The major side effects of diazepam are coughing, respiratory depression, and dyspnea. The respiratory depressant effect of diazepam and other benzodiazepines is dose-dependent and results from depression of the central ventilatory response to hypoxia and hypercapnea. Respiratory depression is more likely to occur in patients with underlying respiratory disease or those receiving combinations of a benzodiazepine and an opioid. Pain at

the site of injection and phlebitis are common after intravenous administration of diazepam.

Midazolam. Midazolam is a water-soluble, short-acting benzodiazepine that was approved for use in the United States in 1986. Midazolam is water-soluble in an acidic solution (pH <3). After intravenous administration, midazolam undergoes an intramolecular reconfiguration at physiologic pH (7.4), increasing its lipid solubility.²⁹ Midazolam is 1.5–3.5 times more potent than diazepam.

Midazolam is distinguished from the other benzodiazepines by its more rapid onset of action and shorter duration of effect. After intravenous administration, the onset of effect for midazolam is 1–2 minutes, and the peak effect is achieved within 3–4 minutes.³⁰ Its duration of effect is 15–80 minutes. Midazolam clearance is reduced in the elderly, obese, and those with hepatic or renal impairment.³¹ The bioavailability of midazolam is increased by approximately 30% in patients using a histamine H₂-receptor antagonist.

Endoscopists prefer the use of midazolam instead of diazepam because of its favorable pharmacologic profile.¹ The initial intravenous dose in healthy adults younger than 60 years of age is 1 mg (or no more than .03 mg/kg) injected over 1–2 minutes.³² Additional doses of 1 mg (or .02–.03 mg) may be administered at 2-minute intervals until adequate sedation is achieved. When midazolam is used with an opioid, a synergistic interaction occurs and a reduction in the dose of midazolam may be indicated. Patients older than 60 and those with ASA physical status III or greater require a dose reduction of 20% or more.²⁹ A total intravenous dose greater than 6 mg usually is not required for routine endoscopic procedures. Patients who are undergoing a prolonged endoscopic procedure and those with a benzodiazepine tolerance may require larger doses.³³

The major clinical applications of midazolam are procedural sedation and induction of general anesthesia. Cole et al³⁴ performed a double-blind, randomized study that compared diazepam with midazolam for endoscopic sedation. Midazolam was found to be more potent and faster acting, reducing the time required for the induction of sedation an average of 2.5 minutes per procedure. Fewer adverse events, including respiratory depression, were reported in the patients receiving midazolam. Midazolam showed superior amnestic properties, and recovery was comparable in the 2 groups. Lee et al³⁵ evaluated midazolam vs diazepam for sedation in 149 patients undergoing EGD. Midazolam was associated with improved patient tolerance, less thrombophlebitis, and more amnesia compared with diazepam. Recovery time was similar with midazolam and diazepam.

The major side effect of midazolam is respiratory depression. Deaths from respiratory depression have been reported in patients receiving midazolam and an opioid.²³ In some cases, apnea may occur as long as 30

minutes after administration of the last dose of midazolam.³⁶ Midazolam-induced respiratory depression may be an administration-related phenomenon, with more rapid administration resulting in a greater number of apneic episodes. Cardiac dysrhythmia has been reported rarely after administration of midazolam.³⁷ Disinhibition reactions, manifested by hostility, rage, and aggression, may occur with benzodiazepines.³⁸

Flumazenil. Flumazenil (1,4-imidazobenzodiazepine), structurally related to midazolam, is a benzodiazepine-specific antagonist. Flumazenil acts at the GABA_A receptor complex to competitively antagonize the central effects of benzodiazepines, reversing sedation, psychomotor impairment, memory loss, and respiratory depression. It is more effective in reversing benzodiazepine-induced sedation and amnesia than respiratory depression.³⁹ Flumazenil is water-soluble and can be administered by either continuous or bolus infusion. The half-life of flumazenil after intravenous administration is .7–1.3 hours, and the average duration of antagonism is 1 hour. Because the effects of midazolam may persist for 80 minutes or longer, re-sedation may occur. Flumazenil also has been shown to reverse ventilatory depression in patients sedated with a combination of benzodiazepine and opioid.⁴⁰ Midazolam-induced reversal of respiratory depression occurs approximately 120 seconds after the intravenous administration of flumazenil.⁴¹

Incremental intravenous boluses of flumazenil of .1–.3 mg are most effective in the treatment of benzodiazepine overdose. Additional boluses or an infusion (.3–.5 mg/h) can be given to prevent patients from relapsing into coma.

Spinelli et al⁴² reported on 51 patients sedated with diazepam who then were randomized to placebo or flumazenil (0.6 mg) after the completion of endoscopy. Compared with placebo, the use of flumazenil improved the level of consciousness and psychomotor activity at 5 minutes, 15 minutes, 30 minutes, and 60 minutes. In another study, Andrews et al⁴³ randomized 50 patients undergoing EGD under midazolam sedation to receive either flumazenil or placebo postprocedure and 30 minutes later. Patients receiving flumazenil (.5 mg) experienced greater improvement in memory, psychomotor performance, and coordination at 5 minutes postprocedure ($P < .001$). Re-evaluation 3.5 hours postprocedure noted no difference in these same measured parameters between the flumazenil and the placebo-treated group. Bartelsman et al⁴⁴ evaluated the use of flumazenil vs placebo in 69 patients sedated with midazolam for EGD. Flumazenil or placebo was administered 15 seconds after completion of the endoscopic procedure. Mean sedation scores returned to baseline within 5 minutes after the administration of flumazenil, and this effect persisted for 60 minutes. No evidence of re-sedation was noted during a 6-hour observation period in patients receiving flumazenil. In summary, the routine administration of fluma-

zenil after the completion of endoscopy reduces recovery time,⁴⁵⁻⁴⁷ although practical benefits for the patient or endoscopy unit have not yet been established.^{43,48,49}

Flumazenil exerts little if any depressant effect on hemodynamic or respiratory parameters. Caution should be exercised when administering this agent to patients using chloral hydrate, carbamazepine, high-dose tricyclic antidepressants, or chronic benzodiazepines because it may induce seizures or withdrawal reaction.⁵⁰

Propofol

Propofol (2,6-diisopropofol) is a hypnotic with minimal analgesic effect. At subhypnotic doses, propofol produces sedation and amnesia.⁵¹ Propofol's hypnotic effect results from potentiation of GABA through a reduction in the rate of GABA-receptor dissociation.⁵² Propofol is highly lipid soluble and has an onset of action equivalent to one arm-brain circulation (30–45 s). It is metabolized rapidly in the liver by conjugation to glucuronide and sulfate to produce water-soluble compounds that are excreted by the kidney. Its duration of effect is 4–8 minutes. The pharmacokinetic parameters of propofol are altered by a variety of factors including weight, sex, age, and concomitant disease; the presence of cirrhosis or renal failure does not significantly affect its pharmacokinetic profile.⁵³ Co-administration of other central nervous system medications such as opioids and barbiturates potentiate the sedative effect of propofol.⁵⁴ The current formulation of propofol contains 1% propofol, 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; propofol should be avoided in persons with allergies to egg, soy, or sulfite. Propofol is not contraindicated in patients with sulfonamide allergy.⁵⁵

The cardiovascular effects of propofol include decreases in cardiac output, systemic vascular resistance, and arterial pressure.⁵⁶ Pain on injection is reported in up to 30% of patients receiving an intravenous bolus of propofol.⁵⁷ Negative cardiac inotropy and respiratory depression can be seen with the use of propofol, although it responds rapidly to a dose reduction or interruption of drug infusion.^{58,59} There have been isolated reports of sepsis resulting from the use of propofol from contaminated vials.

Propofol initially was developed and approved as a hypnotic agent for induction and maintenance of anesthesia. Accordingly, its FDA product label states “[propofol] should be administered only by persons trained in the administration of general anesthesia.” Since approval in the late 1980s, its clinical applications have expanded to include monitored anesthesia care and procedural sedation. Worldwide, the experience with gastroenterologist-directed administration of propofol now exceeds 200,000 patient experiences with no mortalities.⁶⁰⁻⁶³ This, combined with improvements in our understanding of its dosing and titration for moderate sedation, have prompted several professional medical societies to

question the medical necessity of restricting its use to anesthesiologists. The American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy all support gastroenterologist-directed administration of propofol by gastroenterologists. In a joint statement, the 3 societies declared that “with adequate training, physician-supervised nurse administration of propofol can be done safely and effectively.”⁶⁴

Two models have been proposed for the administration of propofol by endoscopists: nurse-administered propofol sedation (NAPS) and combination propofol (also referred to as *multidrug propofol*). Both techniques emphasize several key principles: (1) the use of an established protocol for drug administration, (2) a sedation team with appropriate education and training, and (3) continuous patient assessment of clinical and physiologic parameters throughout the procedure. Several important differences between these 2 models, however, do exist. Table 4 summarizes the important features of both methods of propofol administration.

NAPS. The practice of NAPS involves a trained registered nurse whose sole responsibilities are patient monitoring and the administration of propofol. The published protocols for NAPS differ somewhat with respect to the dosing schedule (Table 5).⁶⁵⁻⁶⁹ Recommendations for the initial bolus of propofol range from 10 to 60 mg, and additional boluses of 10–20 mg are administered with a minimum of 20–30 seconds between doses. Propofol dosing and the depth of sedation are individualized to the needs of each patient. Because propofol possesses no analgesic effect, many patients receiving NAPS will require deep sedation. Heart rate, blood pressure, and pulse oximetry are monitored routinely during NAPS. In most protocols, supplemental oxygen is administered routinely to all patients.

Rex et al⁶⁰ published a retrospective review of more than 36,000 endoscopies performed with NAPS at 3 centers, 2 within the United States and 1 in Switzerland. The targeted depth of sedation was not specified, although the investigators acknowledged that variations in sedation level existed among the 3 sites. The mean doses of propofol at each center were 107, 158, and 245 mg, and 144, 209, and 287 mg, during EGD and colonoscopy, respectively. The rate of clinically important events, defined as an episode of apnea or other airway compromise requiring assisted ventilation (bag-mask), ranged from approximately 1 per 500–1000. In this large case series, endotracheal intubation was not required and no patient suffered permanent injury or death.

Tohda et al⁶⁹ recently reported the results of 27,500 endoscopies performed with NAPS during a 6-year period. These investigators targeted moderate rather than deep sedation. Supplemental oxygen was not provided routinely. The mean doses of propofol during EGD and colonoscopy were 72 and 94 mg, respectively. Notably,

Table 4. NAPS Versus Combination Propofol

	NAPS ^{60,66}	Combination propofol ^{61,71,72,78}
Propofol, mg		
EGD	107–245	35–70
Colonoscopy	144–287	65–100
Supplemental drugs		
Meperidine/fentanyl	No	Yes
Midazolam	No	Yes
Individual(s) responsible for propofol dosing	RN	RN/MD team
Patient monitoring		
Pulse oximetry	Yes	Yes
Blood pressure	Yes	Yes
Electrocardiography	Optional	Optional
Capnography	No	Optional
Staffing requirements	RN dedicated to sedation/monitoring	RN may perform brief interruptible tasks
Induction time, min	2–4	3
Recovery time, min	16–18	14
Target depth of sedation	Deep	Moderate
Rate of cardiopulmonary complication ^a	1–2/1000	0–3.8/1000
Approximate number of published procedures	>200,000	>30,000

RN, registered nurse.

^aCardiopulmonary complication defined as requirement for ventilatory support or pharmacologic intervention for treatment of hypotension or bradycardia.

there were no serious cardiopulmonary events in this series, and no patient required mask ventilation, endotracheal intubation, or any form of resuscitation.

Combination propofol. By combining small doses of several drugs that possess desirable pharmacologic actions, it is possible to maximize the therapeutic actions of each while minimizing the likelihood of a dose-related adverse reaction. *Balanced anesthesia*, the term used to describe this method, is a well-established pharmacologic concept in the practice of anesthesia.⁵⁸

This same pharmacologic principle can be applied to procedural sedation. For example, when propofol is used alone for endoscopic sedation, large doses are required to produce deep sedation and, consequently, dose-related side effects such as hypotension, hypoventilation, or bradycardia are relatively frequent.⁶⁰ In contrast, when

propofol is combined with small doses of an opioid analgesic and a benzodiazepine, analgesia and amnesia can be achieved with subhypnotic doses of propofol, eliminating the need for deep sedation. Furthermore, more precise dose titration is possible with smaller bolus doses of propofol (5–15 mg), and the potential for pharmacologic reversibility is retained using naloxone or flumazenil.^{59,70} Therefore, combination propofol provides the benefits of propofol-mediated sedation while reducing the risk of rapid, irreversible oversedation.⁷¹

The published protocols for combination propofol all include a pre-induction dose of either an opioid (fentanyl, 25–75 μ g; meperidine, 25–50 mg),⁷² a benzodiazepine (midazolam, .5–2.5 mg), or both (Table 5).^{61,73} An induction dose of propofol then is administered (5–15 mg), followed by additional boluses of 5–15 mg titrated

Table 5. Selected Series of Gastroenterologist-Directed Administration of Propofol

Author	Year	No. patients	Initial dose, mg	Mean propofol dose			Fentanyl, mcg	Midazolam, mg
				Subsequent dose, mg	Cumulative dose, mg			
NAPS								
Wehrman ⁶⁸	1999	198	40–60	20	388	—	—	
Rex ⁶⁵	2002	2000	20–40	10–20	CL, 242; EGD, 190	—	—	
Walker ⁶⁶	2003	9152	30–50	10–20	CL, 210; EGD, 150	—	—	
Heuss ^{67,a}	2003	2574	20	10–20	106–163 ^b	—	—	
Combination propofol								
Clarke ⁶¹	2002	28,472	20–40	10–30	CL, 67; EGD, 34	25–75	2–5	
Paspatis ⁷⁸	2002	64	20	20	80	—	2–3	
Cohen ⁷³	2003	819	10–15	5–15	CL, 66; EGD, 52	50–75	.5–1.0	

CL, colonoscopy.

^aSelect patients undergoing colonoscopy received meperidine 12.5–25 mg.

^bCalculation based on a 70-kg patient.

to effect. Most protocols target moderate rather than deep sedation.^{61,71,74} The average cumulative doses of propofol in a combination regimen are 65–100 mg and 35–70 mg during colonoscopy and EGD, respectively. A nurse has primary responsibility for monitoring the patient; however, in contrast with NAPS, both the nurse and the endoscopist participate in all dosing decisions that involve propofol. Furthermore, the nurse responsible for sedation also may perform brief, interruptible tasks such as assisting with tissue acquisition. Clinical and physiologic parameters are monitored in all cases, and in some instances capnography is used as well.⁷³

Several studies have reported results using a multidrug regimen. Clarke et al⁶¹ reported a 7-year experience with more than 28,000 procedures using a combination of propofol, fentanyl, and midazolam. Moderate sedation was targeted during each procedure. There were no deaths or endotracheal intubations in this series. In another series, Rudner et al⁷⁴ compared the results of sedation with remifentanyl plus low-dose propofol (mean doses, 230 μ g and 47 mg) (sedation group) with a group of patients receiving “total intravenous anesthesia” (TIVA) using propofol, fentanyl, and midazolam (mean doses, 85 mg, 140 μ g, and 3.4 mg) (TIVA group). Patients in the sedation group were assessed to be sedated moderately based on their ability to “communicate at any time during the procedure,” and the bispectral index (BIS). These and other studies support the observation that propofol, combined with an opioid and benzodiazepine, is an effective and safe method of sedation when administered by an endoscopist with adequate training.⁷³

At least 10 randomized trials have compared the safety and effectiveness of propofol (monotherapy) with traditional sedation agents (excluding studies that use patient-controlled delivery). Wehrmann et al⁶⁸ compared propofol (mean dose, 388 mg) with midazolam (mean dose, 7.8 mg) in 198 consecutive patients undergoing endoscopic retrograde cholangiopancreatography. Endoscopists preferred propofol to midazolam, presumably because of deeper sedation and improved patient cooperation. Nonetheless, patient satisfaction in the 2 sedation groups was comparable. In addition, although the frequency of cardiopulmonary events was comparable in both groups, 1 patient receiving propofol experienced an episode of apnea requiring bag-mask ventilation. Vargo et al⁷⁵ compared propofol (mean dose, 356 mg) with meperidine and midazolam (mean doses, 108 mg and 8.4 mg; calculation based on a 70-kg patient) in 75 patients undergoing endoscopic retrograde cholangiopancreatography or endoscopic ultrasonography. The dosing of propofol was titrated carefully using capnography. Patient satisfaction and physiologic parameters were similar in both sedation groups. Rex et al performed 2 trials comparing NAPS with traditional sedation agents; the mean doses of propofol, midazolam/meperidine (or fentanyl) were 218 mg, 4.7 mg/90 mg, and 277 mg, 7.2

mg/117 μ g, respectively.^{76,77} Although the first of these studies reported improved satisfaction scores in the group receiving propofol,⁷⁶ patient satisfaction between groups was comparable in the second trial.⁷⁷ Throughout these studies, the mean recovery and discharge times are consistently lower with propofol than traditional sedation drugs.

There are few published studies that directly compare combination propofol with standard sedation agents. Paspatis et al⁷⁸ studied propofol plus midazolam (mean doses, 80 and 3 mg) vs midazolam and pethidine (mean doses, 5 and 75 mg) in 120 patients undergoing colonoscopy. Patients receiving propofol were more likely to report no discomfort during their procedure (84.3% vs 66%, $P < .05$) and recovered faster. No difference in the rate of cardiopulmonary complications was observed. Koshy et al⁷² evaluated propofol combined with fentanyl (median doses, 40 mg and 50 μ g) vs midazolam and meperidine (dose range, 2–6 mg and 25–75 mg) in 274 nonrandomized patients undergoing colonoscopy or EGD. The use of propofol was associated with better patient comfort ($P = .03$) and deeper sedation. Recovery time and cardiopulmonary complications were similar within the 2 study groups. Reimann et al⁷⁹ randomized 79 patients undergoing colonoscopy to receive sedation either with propofol plus midazolam (median doses, 100 and 2 mg) or midazolam (median dose, 9 mg) either alone or combined with nalbuphine (median dose, 20 mg). Patients in the propofol group were more likely to rate their procedure as comfortable (81% vs 47%, $P = .02$), and recovery time was shorter (12 vs 93 min, $P < .001$). There was no difference in the cardiorespiratory parameters between the 2 groups.

Qadeer et al⁸⁰ assessed the comparative safety of propofol and benzodiazepine/opioid sedation (both administered under the direction of a gastroenterologist) in a recent meta-analysis of 12 randomized controlled trials. A total of 1162 patients were included in the analysis, 634 received propofol and 527 received midazolam/opioid. Hypoxemia and hypotension were used as study end points. For colonoscopy and EGD, the pooled odds ratios for hypoxemia or hypotension were .4 (95% confidence interval, .2–.79) and .74 (95% confidence interval, .44–1.44), respectively. These findings indicate that for the parameters analyzed, gastroenterologist-directed propofol sedation was at least as safe as conventional sedation.

There is widespread belief among gastroenterologists that propofol provides better sedation for endoscopy than an opioid/benzodiazepine combination. Its benefits over traditional sedation agents are believed to include faster recovery, improved sedation effect, and greater efficiency within the endoscopy unit. Although comparative trials have shown propofol's clear-cut superiority in terms of recovery time and physician satisfaction, similar improvement in patient satisfaction has been more difficult to prove. At the current time, until randomized

studies demonstrate which sedation agent(s) and method of administration are best suited to endoscopy, endoscopists are recommended to review the published literature and practice guidelines pertaining to endoscopic sedation and then to choose a method of sedation that they are comfortable with and that meets the needs of their patients. Gastroenterologists electing to use propofol should acquire the necessary training and experience before implementing a propofol sedation program within their facility.

Other Agents

Ketamine. Ketamine is a phencyclidine derivative that has been available since 1970. Unlike other sedation drugs, ketamine possesses both analgesic and sedative properties. Ketamine causes functional dissociation between the limbic and cortical systems, selectively depressing the cortex and thalamus while stimulating parts of the limbic system. A trance-like cataleptic state is produced that impairs sensory recognition of painful stimuli and memory.⁸¹

After intravenous administration, ketamine has a rapid onset of action (<1 min) and short duration of effect (10–15 min).⁸² Ketamine is easy to administer, and in contrast to benzodiazepine/narcotic regimens, does not depress airway or cardiovascular reflexes. When ketamine was administered inadvertently to 9 children at doses 5–100 times greater than that intended, only brief respiratory depression was observed.⁸³

The use of ketamine for endoscopic sedation has been studied predominantly in the pediatric setting. In a retrospective review of children ranging in age from 1 month to 20 years, a combination of ketamine and midazolam (N = 128) was compared with 2 alternative regimens, midazolam and meperidine (N = 192), and midazolam, meperidine, and ketamine (N = 82).⁸⁴ The standard dose range for each drug was midazolam (.05–.2 mg/kg), meperidine (1.0–2.0 mg/kg), and ketamine (.75–2.0 mg/kg) per dose. Inadequate sedation was less frequent with ketamine/midazolam than either of the other sedation groups (3.1% vs 8.9% and 8.6%, $P = .07$). Complications, predominately hypoxemia, were significantly more common with midazolam/meperidine than in either of the ketamine arms. A single patient in the ketamine group (1 of 128; <1%) experienced transient hypoxemia, and there were no serious adverse events. In another study, Aggarwal et al⁸⁵ reported on 226 pediatric patients undergoing upper endoscopy, colonoscopy, or endoscopic sclerotherapy sedated with atropine, ketamine, and midazolam. The majority of patients achieved complete recovery within 15 minutes. There were no episodes of clinically significant respiratory depression or cardiovascular instability. In adults, ketamine has been useful as an adjunct to standard sedation for difficult-to-sedate patients.⁸⁶ Despite its success as a sedation agent for children, the use of ketamine in adults has been

limited. Possible reasons for this include a lack of experience among endoscopists and concern over emergence reactions.

Ketamine produces a dose-dependent increase in heart rate, blood pressure, and cardiac output, mediated through stimulation of the sympathetic nervous system. Consequently, its use potentially is dangerous and should be avoided in patients with ischemic heart disease, cerebrovascular disease, or hypertension. Emergence reaction, manifested by floating sensations, vivid dreams, hallucinations, and delirium, has been reported in 10%–30% of adults. The use of midazolam in combination with ketamine is reported to minimize this reaction.⁸⁷

Nitrous oxide. Nitrous oxide is an inhalational agent co-administered with oxygen. After inhalation, nitrous oxide rapidly crosses the blood-brain barrier, accounting for its rapid onset of action. The gas is cleared quickly and excreted unchanged by the lungs. The benefits of nitrous oxide include rapid onset, rapid recovery, and an excellent safety profile.

Saunders et al⁸⁸ performed a randomized, placebo-controlled trial of patient-controlled nitrous oxide vs intravenous pethidine and midazolam (mean doses, 50 and 2.5 mg) in patients undergoing colonoscopy. Procedure-related discomfort was comparable between study groups. Patients receiving intravenous sedation experienced more prolonged sedation and slower recovery than the nitrous oxide group (60 vs 32 min, $P = .001$). Hypotension and oxygen desaturation were more common with intravenous sedation than nitrous oxide, and many in the nitrous oxide group experienced headache. In another study, Forbes and Collins⁸⁹ randomized patients undergoing colonoscopy to sedation using nitrous oxide or intravenous meperidine and midazolam (mean doses, 55 and 4.7 mg). Overall, nitrous oxide was less effective than intravenous sedation; patients receiving nitrous oxide recalled more pain and were less satisfied with the procedure (33 vs 3, $P < .0001$; 13 vs 6, $P = .01$, respectively). Recovery was shorter in the nitrous oxide group compared with those receiving intravenous sedation (30 vs 60 min, $P < .0001$).

Maslekar et al⁹⁰ recently reported the results of a randomized, controlled study that compared nitrous oxide with intravenous fentanyl and midazolam. One hundred twenty patients undergoing colonoscopy were randomized. Patients in the nitrous oxide arm all completed colonoscopy without supplemental medications, and scored better with respect to overall satisfaction and the assessment of pain. The time to discharge was significantly shorter in the nitrous oxide arm (26 vs 44 min; $P = .0004$).

Nitrous oxide may have potential value for endoscopic sedation. In previous studies, some patients receiving this agent have required intravenous sedation to complete their examination. Headache has been a troubling side effect of nitrous oxide in several studies. Large-scale clin-

ical trials comparing nitrous oxide with intravenous sedation across a variety of patient populations are necessary before its use can be recommended.

The major risk of nitrous oxide is hypoxia, which is avoided by co-administration with 30%–50% oxygen. Hypertension, arrhythmias, nausea, vomiting, and headache also have been reported with nitrous oxide. The relationship between nitrous oxide and malignant hyperthermia is disputed within the literature.^{91,92}

Dexmedetomidine. Dexmedetomidine is an α_2 -adrenoreceptor agonist with a mechanism of action that is unique among sedative agents. It inhibits neuronal activity in the brain and spinal cord by activation of α_2 -receptors, producing sedative, analgesic, anxiolytic, and sympatholytic effects. Unlike other sedative agents, patients sedated with dexmedetomidine return to their baseline level of consciousness when stimulated.⁹³ Dexmedetomidine also produces less respiratory depression than other sedative agents.⁹⁴ The pharmacologic effects of dexmedetomidine can be reversed by the α_2 -receptor antagonist atipamezole.⁹⁵ These beneficial properties make dexmedetomidine an attractive agent for short-term procedural sedation. The usual dose of dexmedetomidine for procedural sedation is 1 $\mu\text{g}/\text{kg}$, followed by an infusion of .2 $\mu\text{g}/\text{kg}/\text{h}$. Its onset of action is less than 5 minutes and the peak effect occurs within 15 minutes.

Two large, double-blind, placebo-controlled trials have assessed the efficacy of dexmedetomidine in postsurgical patients requiring ventilation and sedation. In both studies, dexmedetomidine resulted in significantly less use of rescue midazolam or propofol than placebo.^{96,97} Jalowiecki et al⁹⁸ randomized patients undergoing colonoscopy to dexmedetomidine (1 $\mu\text{g}/\text{kg}$ followed by .2 $\mu\text{g}/\text{kg}/\text{h}$) vs meperidine (1 mg/kg) and midazolam (.05 mg/kg) vs on-demand fentanyl (.1–.2 mg). Forty-seven percent of patients receiving dexmedetomidine required supplemental fentanyl to achieve satisfactory analgesia. Hypotension (4 of 19; 21%), bradycardia (2 of 19; 10%), and vertigo (5 of 19; 26%) were reported in the group receiving dexmedetomidine. Recovery time was longest (85 min) in patients receiving dexmedetomidine.

Dexmedetomidine has a biphasic cardiovascular effect. After administration of a 1- $\mu\text{g}/\text{kg}$ bolus, there is a transient increase of the blood pressure in response to stimulation of the peripheral α_2 -adrenoreceptors. Within 5–10 minutes, the blood pressure then decreases 10%–20% as a result of inhibition of the central sympathetic outflow. In addition to its effect on blood pressure, other adverse effects include bradycardia, nausea, atrial fibrillation, and hypoxia.⁹⁹

Diphenhydramine. Diphenhydramine hydrochloride is a histamine H_1 -receptor antagonist with anticholinergic and sedative properties. It has been used in the treatment of allergic symptoms and as an adjunct for

sedation in dental, ophthalmologic, and endoscopic procedures.

The usual dose of intravenous diphenhydramine as an adjunct for endoscopic sedation is 25–50 mg. Diphenhydramine is distributed quickly through the body, including the central nervous system.¹⁰⁰ Its onset of action is several minutes and duration of effect is up to 4–6 hours. Its hypnotic effect is increased when given in combination with alcohol or other central nervous system depressants such as benzodiazepines or opioid narcotics. Diphenhydramine has a modest stimulatory effect on ventilation, and has been reported to counteract opioid-induced hypoventilation.¹⁰¹

Tu et al¹⁰² assessed diphenhydramine as an adjunct to meperidine and midazolam during colonoscopy in a randomized, double-blind trial. Two hundred seventy patients received either diphenhydramine 50 mg or placebo intravenously 3 minutes before initiating sedation. Patient scores for overall sedation were better in the group receiving diphenhydramine (9.4 vs 9.04, $P = .017$). Further, the diphenhydramine group required less meperidine (89.7 vs 100 mg, $P = .003$) and midazolam (3.4 vs 4.0 mg, $P < .001$). Procedure, recovery, and discharge times were comparable between both groups.

The adverse effects of diphenhydramine include hypotension, dizziness, blurred vision, dry mouth, epigastric discomfort, urinary retention, and wheezing.¹⁰³

Promethazine. Promethazine is a phenothiazine that possesses antihistamine, sedative, anti-emetic, and anticholinergic effects. It has been used for the management of allergic reactions and anaphylaxis, as treatment of postoperative nausea and vomiting, and as an adjuvant for postoperative pain and sedation. Promethazine also has been investigated as an adjunct for sedation during minor surgical and endoscopic procedures.¹⁰⁴

Promethazine blocks postsynaptic dopaminergic receptors in the brain and has a strong α -adrenergic inhibitory effect. In addition, it is a competitive histamine H_1 -receptor antagonist and blocks most, but not all, of the pharmacologic effects of histamine mediated at H_1 receptors. The clinical effects of promethazine are evident within 5 minutes of intravenous administration. Its duration of action is 4–6 hours and its plasma half-life is 9–16 hours.

The usual dose of promethazine is 12.5–25 mg intravenously, infused slowly (≤ 25 mg/min) to minimize the risk of hypotension.¹⁰⁵ A total dose of 25–100 mg may be used as an adjuvant to narcotics and benzodiazepines. The use of promethazine may require a reduction in the dosage of standard sedation agents.

Findlay¹⁰⁶ evaluated the use of promethazine in 100 patients undergoing endoscopy or bronchoscopy. Promethazine (25–100 mg intramuscularly) was administered in combination with meperidine. All but one of the procedures was completed and there were no episodes of hypotension. Nine patients were reported to be unco-

operative during their procedure, and 2 patients experienced confusion. There were no episodes of respiratory failure.

The adverse effects of promethazine include hypotension, respiratory depression, neuroleptic malignant syndrome, and extrapyramidal effects that range from restlessness to oculogyric crises.¹⁰⁷

Droperidol. Droperidol, a fluorinated derivative of the phenothiazines, acts centrally by occupying GABA receptors on the postsynaptic membrane. It is a potent anti-emetic and central nervous system depressant, inducing a cataleptic state of immobility. Droperidol has been used in the perioperative period as an anti-emetic and sedative, for treatment of opioid-induced pruritus, and as an adjunct to standard sedation for complex endoscopic procedures or difficult-to-sedate patients such as alcoholics and chronic drug abusers.¹⁰⁸⁻¹¹⁰

Droperidol's onset of action is 3-10 minutes and its duration of effect is 2-4 hours.¹¹¹ The usual dose of droperidol for endoscopic sedation is 1.25-2.5 mg intravenously, although higher doses have been used. A dose reduction is recommended in patients with renal or liver disease.

Lebrun¹¹² reported the first large series using droperidol for endoscopic sedation. Patients achieved adequate sedation for upper endoscopy, although 24% experienced transient hypotension. No major complications were reported. In another study, 60 difficult-to-sedate patients undergoing EGD were sedated with either fentanyl/diazepam or fentanyl/droperidol.¹¹³ Sedation under fentanyl/droperidol was assessed to be better than the diazepam/fentanyl combination.

Wilcox et al¹⁰⁹ used droperidol as an adjunct to standard sedation in 764 patients undergoing 1102 endoscopic procedures. The indications for droperidol included active alcohol withdrawal, patients who were difficult-to-sedate during a previous endoscopic examination, and chronic narcotic and/or intravenous drug users. The total dose of droperidol ranged from 1.25 to 5.0 mg intravenously. Hypotension was the most common complication. No patient experienced respiratory depression requiring ventilatory support.

Hypotension, prolongation of the QT_c interval, and extrapyramidal signs are the major side effects of droperidol. In 2001, the FDA added a black-box warning to the FDA product label, indicating that droperidol should be used only when first-line drugs are unsuccessful.¹¹⁴ Droperidol use is contraindicated in patients with a prolonged QT_c interval (>440 ms in males, >450 ms in females), and should be avoided in patients at increased risk of developing QT interval prolongation (history of congestive heart failure, bradycardia, diuretic use, cardiac hypertrophy, hypokalemia, hypomagnesemia, ≥65 years of age, and alcohol abuse).¹¹⁵ In view of the recent change in product labeling and the availability of shorter-acting

sedatives, the use of droperidol as an adjunct for endoscopic sedation should be avoided in most circumstances.

Summary Statements and Recommendations

3. The endoscopist should be familiar with the pharmacokinetic and pharmacodynamic properties as well as potential drug-drug interactions of all agents used for sedation and reversal. An understanding of the time to peak effect is especially important to avoid oversedation during the induction phase of sedation.
4. The majority of patients can be sedated adequately by using a combination of an opioid and a benzodiazepine. The addition of an adjunctive agent in combination with conventional sedation drugs may be useful for the difficult-to-sedate patient.
5. Gastroenterologist-directed administration of propofol is a safe and effective alternative to sedation with opioids and benzodiazepines. Specialized training is required for the physician and nursing staff before instituting a propofol sedation program.

Patient Monitoring

Patient monitoring is an essential element of endoscopic sedation. The term *monitoring* includes both visual assessment as well as the use of devices to measure physiologic parameters. A trained observer may recognize subtle alterations in the patient's condition before objective changes are detected in vital signs and other parameters.

Guidelines for patient monitoring during endoscopic procedures have been developed by several professional medical societies.^{5,45,116} The American Society of Gastrointestinal Endoscopy training guidelines state that an endoscopic trainee must know the appropriate role of monitoring devices for sedation, including pulse oximetry and selective use of continuous electrographic and blood pressure monitoring. Before sedating the patient, all monitoring and resuscitation equipment required for the intended level of sedation should be present and functioning.

Personnel and Emergency Equipment

A nurse or assistant with appropriate training in endoscopic sedation should be present throughout the endoscopic procedure. This individual should have an understanding of the stages of sedation, an ability to monitor and interpret the patient's physiologic parameters, skills to initiate appropriate intervention in the event of a complication, and current certification in basic or advanced cardiac life support. During moderate sedation, the person assigned responsibility for patient assessment also may perform tasks that are interruptible and of short duration. When deep sedation is planned, this individual should be dedicated to observation and monitoring and have no other procedure-related responsibilities.

Table 6. Emergency Resuscitative Equipment

Assorted syringes, tourniquets, adhesive tape
Intravenous access equipment including fluids
Basic airway management equipment
Oxygen supply
Suction machine and catheter
Nasal cannulae and face-masks ^a
Bag-mask ventilation device
Oral and nasal airways (all sizes)
Advanced airway management equipment
Laryngoscope handles and blades ^a
Endotracheal tubes and stylets ^a
Laryngeal mask airway ^a
Cardiac equipment
Pulse oximeter
Cardiac defibrillator
Emergency medications
Atropine
Diphenhydramine
Epinephrine
Ephedrine
Flumazenil
Glucose, 50%
Hydrocortisone
Lidocaine
Naloxone
Sodium bicarbonate

^aAll appropriate sizes should be available.

ities. At least one member of a sedation team should be certified in advanced cardiac life support and capable of establishing an airway and providing positive-pressure ventilation.

A list of emergency equipment is provided in Table 6. This equipment should be immediately available whenever sedation and analgesia are being administered. The equipment stocked on an emergency cart should be tailored to the practice environment and the training of the sedation team. For example, practices that perform endoscopy and sedation on pediatric patients will need to stock equipment that is size-appropriate. It is strongly recommended that a cardiac defibrillator be available on-site. Equipment for providing positive-pressure ventilation must be immediately available. The required items include oral and nasal airways and an ambu-bag. Advanced airway management equipment including laryngoscopes and endotracheal tubes, or laryngeal mask airways may be appropriate elements of an emergency cart.

Continuum of Sedation

Sedative and/or analgesic agents produce alterations in a patient's level of consciousness. These changes in consciousness occur along a continuum that range from anxiolysis to general anesthesia. Four stages of sedation have been defined: minimal, moderate, deep, and general anesthesia (Table 7).⁵ These levels are defined by a stimulus-response relationship: does the patient show purposeful response (verbal or nonverbal) to verbal cues, light tactile stimuli, brusque shaking, or pain? The

risk of hemodynamic instability and hypoventilation usually are limited to deep sedation and general anesthesia; consequently, nonanesthesiologists are advised to perform surgery within minimal to moderate sedation.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Thus, individuals who administer moderate or deep sedation must be competent to administer reversal agents, manage an airway, and provide advanced cardiac life support (ACLS) care.

A patient's level of consciousness should be assessed and documented, beginning before the initiation of sedation and continuing throughout the procedure and recovery period, until the patient is suitable for discharge. Several sedation scales and scoring systems have been developed to describe the level of consciousness.¹¹⁷⁻¹¹⁹ An ideal sedation assessment tool should be easy to use, capable of being administered quickly, and its results should be reproducible across observers and various patient populations. No such instrument currently exists. The (modified) Observer's Assessment of Alertness and Sedation is the sedation scale that currently is used most often in clinical research (Table 8).

Hemodynamics and Electrocardiography

Heart rate and blood pressure are important parameters of circulatory stability, providing information regarding the patient's baseline condition and the effects of sedation. For example, baseline tachycardia and hypotension in a patient presenting for colonoscopy is likely to represent volume depletion resulting from catharsis and/or inadequate oral hydration. These hemodynamic parameters also provide important feedback during an endoscopic procedure. Tachycardia and hypertension may indicate that the patient is sedated inadequately, whereas bradycardia and/or hypotension may be an early indication of oversedation.

Automated noninvasive blood pressure devices are now used widely. In addition to providing systolic, diastolic, and mean arterial pressure, they have audible alarms to alert personnel if the reading is outside of acceptable limits and provide a permanent record of recorded data. All patients receiving intravenous sedation should be monitored for heart rate and blood pressure. A baseline blood pressure should be noted before the administration of sedation, and then at 3- to 5-minute intervals throughout the procedure.

The role of continuous electrocardiography during endoscopic sedation has not been established. Initially, its use was intended to detect arrhythmias in high-risk patients undergoing deep sedation, monitored anesthesia care, or general anesthesia. The ASA practice guidelines indicate that patients with significant cardiovascular dis-

Table 7. Levels of Sedation and Analgesia

	Minimal sedation (anxiolysis)	Moderate sedation/analgesia (conscious sedation)	Deep sedation/analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful ^a response to verbal or tactile stimulation	Purposeful ^a response following repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation/analgesia (conscious sedation) is a drug-induced depression of consciousness during which patients respond purposefully^a to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully^a 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 drug-induced 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.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Individuals administering moderate sedation/analgesia (conscious sedation) should be able to rescue patients who enter a state of deep sedation/analgesia, while those administering deep sedation/analgesia should be able to rescue patients who enter a state of general anesthesia.

^aReflex withdrawal from a painful stimulus is NOT considered a purposeful response.

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ease or dysrhythmia should have electrocardiographic monitoring during endoscopic sedation.⁵ In contrast, an evidence-based analysis of the literature recently concluded “there is no evidence that cardiac monitoring during procedural sedation and analgesia is of benefit, especially if the patient has no underlying cardiopulmonary disease.”¹⁰ The use of continuous electrocardiography during routine endoscopic procedures in low-risk patients is not required. High-risk patients (including those with a history of dysrhythmias) receiving sedation should be considered for cardiac monitoring.

Pulse Oximetry

Pulse oximetry is a noninvasive method for continuous measurement of arterial hemoglobin oxygen saturation and heart rate. The relationship between hemo-

globin saturation and arterial oxygen partial pressure is defined by the sigmoid-shaped oxyhemoglobin dissociation curve. During normal respiration with oxygen saturation levels approaching 100%, significant changes in arterial oxygen partial pressure may occur with little alteration in oxygen saturation. In the event of hypoventilation, the oxygen saturation will maintain a level of 90% or more until the arterial oxygen partial pressure decreases to less than 70 mm Hg. Consequently, measurement of oxygen saturation is relatively insensitive to the earliest signs of hypoventilation. The administration of supplemental oxygen further delays the detection of hypoventilation. Other limitations of oximetry include the inability to detect an adequate signal during hypothermia, low cardiac output, and motion (eg, tremor). For these reasons, the use of pulse oximetry should supplement, rather than replace, direct observation of the patient's respiratory effort.

Numerous studies have shown the ability of pulse oximetry to detect desaturation in the setting of procedural sedation. The clinical significance of transient desaturation, however, remains uncertain. Furthermore, the ability of oximetry to reduce the incidence of cardiopulmonary complications remains unproven. Nonetheless, most experts agree that pulse oximetry should be monitored routinely in patients receiving intravenous sedation for endoscopic procedures.

Table 8. Modified Observer's Assessment of Alertness/Sedation Scale

Responsiveness	Score
Agitated	6
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

Capnography

Capnography is a noninvasive technique used to quantitate CO₂ in expired gases, providing a sensitive measure of ventilatory function. Capnography may detect hypoventilation before pulse oximetry indicates a decrease in oxygen saturation.¹²⁰ Studies confirm that capnography is also a more sensitive measure of alveolar hypoventilation than visual observation.^{121,122}

Sidestream capnography uses an infrared measuring cell to analyze the CO₂ content of sampled gas. The sampling probe for procedural sedation usually consists of a nasal cannula, sometimes combined with an additional probe to sample gas from the mouth. An additional port allows supplemental oxygen to be administered through the same cannula. An aspiration port permits continuous sampling of patient gases during inspiration and expiration. The most common visual display of capnographic data is CO₂ vs time, referred to as the *capnographic waveform* or *capnogram*. The normal capnograph wave peaks during expiration whereas the trough occurs during inspiration. There are specific waveform patterns that may be used to identify patterns of respiration.

Changes in end-tidal CO₂ denote an alteration in the patient's ventilatory status, and provide an opportunity to recognize hypoventilation earlier than either visual assessment or pulse oximetry.¹²¹⁻¹²³ The clinical relevance of this information, however, is uncertain. The ASA concluded that CO₂ monitoring "should be considered for all patients receiving deep sedation and for patients whose ventilation cannot be observed directly during moderate sedation."⁵ Currently, there is insufficient evidence in the literature to support its use routinely during endoscopic sedation.

BIS

BIS monitoring is a noninvasive method of assessing a patient's level of consciousness. The BIS monitor is a bedside device that records electroencephalographic waveforms from a self-adhesive forehead probe. Electroencephalographic activity provides a sensitive measure of sedation, changing from a low-amplitude, high-frequency signal in the awake state to a high-amplitude, low-frequency signal during anesthesia. The BIS monitor uses a complex algorithm to analyze the electroencephalogram, generating a BIS index that ranges from 0 to 100.⁸ A BIS index between 70 and 90 corresponds to moderate sedation, between 60 and 69 is deep sedation, between 40 and 59 is general anesthesia, and less than 40 denotes deep hypnosis.¹²⁴

The BIS monitor was approved in 1996 as a consciousness monitor for use during general anesthesia. Since that time, its use has expanded into the outpatient setting. Several studies have shown a correlation of the BIS with validated sedation scales.¹²⁵⁻¹²⁷ Observational studies indicate that a BIS index of 80-85 corresponds to the

optimal level of sedation during endoscopy performed under an opioid and benzodiazepine.^{128,129} A study of 102 patients undergoing colonoscopy failed to show the usefulness of the BIS during NAPS.¹³⁰ At the current time, the role of BIS monitoring during moderate sedation remains uncertain.¹³¹

Supplemental Oxygen

The routine administration of supplemental oxygen during moderate and deep sedation is endorsed by the ASA as well as the American Society of Gastrointestinal Endoscopy. The ASA guidelines state "supplemental O₂ should be considered for moderate sedation and should be administered during deep sedation unless specifically contraindicated for a particular patient or procedure."⁵ The American Society of Gastrointestinal Endoscopy position states "supplemental O₂ administration has been shown to reduce the magnitude of oxygen desaturation when given during endoscopic procedures."⁴⁵ Nonetheless, there is little evidence in the literature that this practice reduces the incidence of significant cardiopulmonary complications in patients monitored with pulse oximetry. Furthermore, numerous studies have indicated that administration of supplemental O₂ actually may delay recognition of hypoxemia and apnea, potentially increasing the rate of sedation-related complications.¹³²⁻¹³⁵ The use of supplemental oxygen during endoscopy is recommended for elderly patients and those with significant comorbid disease (ASA class IV and V). Equipment to administer supplemental oxygen should be available wherever endoscopic sedation is being delivered.

Summary Statements and Recommendations

6. Personnel who administer sedation agents should possess the ability to recognize and rescue patients whose level of sedation becomes deeper than originally intended.
7. The use of noninvasive blood pressure monitoring devices, measurement of oxygen saturation, and other devices are supplemental to clinical observation of the patient.
8. New methods of monitoring are undergoing clinical evaluation. These monitoring devices have not yet undergone rigorous study to assess their impact on clinical outcomes, and their routine use for moderate sedation cannot be recommended based upon the current literature.

Training Guidelines

The training process should provide the skills necessary to administer endoscopic sedation safely and effectively. This requires the following: (1) an understanding of the pharmacologic principles of the drugs used for sedation and analgesia, (2) an ability to monitor sedated patients, and (3) the resources to manage com-

plications that may occur. In addition to the skill sets listed earlier, the endoscopist should possess a thorough understanding of the preprocedural assessment and be able to properly identify those patients who represent above-average risk for a cardiopulmonary complication (see Preprocedure Assessment).

Little research has been conducted on the topic of training in sedation for endoscopic procedures. Nonetheless, training guidelines for the didactic and practical education of sedation have been proposed by various professional societies.^{10,45,116} The didactic portion of training may be in the form of lectures, topic reviews at academic conferences, or independent study. Practical training, generally performed in the context of training for gastrointestinal endoscopy, usually is completed in the endoscopy unit of the training institution under the supervision of the endoscopy instructor. Training under the guidance of an anesthesiologist or an anesthesia department generally has not been required.

The use of patient simulators for training and competency assessment in medicine is evolving rapidly, particularly in the field of anesthesia.^{5,136} The new generation of simulators provide for patient simulation, a workplace environment with either hardware or electronic output displays (ie, pulse oximetry, capnography, and so forth), an interface component that permits input, and software programs with physiologic and control logic that enable the simulator to respond appropriately to input from the trainee and instructor.¹³⁷ In the future, it is likely that simulator training will become an integral component of sedation instruction for physicians who wish to acquire new skills or obtain recertification.

Moderate Sedation

Didactic training for endoscopic sedation should begin with the definitions for various forms and levels of sedation. Moderate sedation provides for the administration of sedative and analgesic medication, during which time the patient remains able to respond purposefully to verbal and/or non-noxious tactile stimulation.⁵ This and other levels of sedation have been defined elsewhere in this article (see Continuum of Sedation). Instruction should include a detailed discussion of the pharmacology of specific sedative and analgesic medications and their indications, doses, and side effects. The use of multiple pharmacologic agents and the practice of titration to desired effect also should be illustrated, especially with regard to the potential for drug synergism and its impact on cardiorespiratory function. Trainees in endoscopy also should undergo instruction regarding pharmacologic agents used to counteract the effects of benzodiazepines and narcotics, specifically the antagonists flumazenil and naloxone.

The initial evaluation of patients before sedation should be discussed, including the preprocedural history and physical examination (see Preprocedural Assess-

ment). The identification of existing cardiac or pulmonary disease before the procedure is essential to correctly triage the patient to the location that is most appropriate for the procedure (endoscopy suite, intensive care unit, operating room). Current medication should be elicited, as well as any history of adverse reactions to anesthesia. The ASA physical status should be assessed. Physical examination should include not only the pulmonary and cardiac status, but also describe the Mallampati score, based on oropharyngeal anatomy that indicates the potential difficulty of intubation if required. Informed consent should not be limited to a signature on a standard form, but rather taught as a process during which the indications, risks, benefits, alternatives, and expected outcomes are explored in detail with the patient (see Medical-legal Considerations). Confirmation of an escort for outpatients should be provided, and the sedation plan should be discussed and documented.

Proper monitoring of patients during sedated procedures should be stressed, including the necessity for personnel whose primary function is the administration and monitoring of sedative medication. Full understanding of the use of automated monitoring devices and interpretation of the findings is required (see Patient Monitoring). Training also should include recognition of sedation complications such as cardiopulmonary compromise. As per Joint Commission requirements, at least one individual involved with sedated endoscopy should be certified in advanced cardiac life support; however, it is recommended that both the endoscopist as well as the endoscopy nurse attain certification. Training should include airway management and respiratory support, and personnel should demonstrate competence to assess the patient's ventilatory status. Training in airway support includes techniques such as jaw-thrust and chin-lift maneuvers, oral and nasal airway insertion, and bag-mask ventilation. Practitioners should demonstrate the ability to establish an airway and provide positive-pressure ventilation. Differentiation between oxygenation and ventilation should be highlighted and the use of supplemental oxygen should be discussed. Resources to treat patients who experience complications of sedation and/or endoscopy should be immediately available, including antagonists for sedative and analgesic medication, equipment for ventilation and oxygenation, and an electrical defibrillation device.

Specific numbers of sedated procedures required for competence in endoscopic sedation have not been established; however, this may be construed as similar to endoscopic assessment, for which guidelines for procedure volume have been published.

Assessment of the skills acquired through training in endoscopic sedation may be obtained through objective criteria to document competence in sedation (ie, written and/or verbal testing), subjective opinion of endoscopy instructors or the institutional training program direc-

tor, and through the hospital credentialing system. Monitoring of sedation skills may be conducted through the hospital quality-improvement process. Specific outcomes related to sedation should be assessed, including cardiopulmonary compromise and emergency intervention, the use of antagonist medication, unplanned procedure termination, unplanned hospital admission or transfer to critical care, and mortality related to endoscopic procedures.

Deep Sedation

The requirements of a specialized training program for the use of propofol, in addition to the training already required for moderate sedation, remains an area of uncertainty.¹³⁸ The pharmacologic properties of propofol should be discussed, including the potential for rapid transition between levels of sedation. As with moderate sedation, personnel should be familiar with the resuscitation of patients who become unresponsive, unable to protect their airway, or lose spontaneous respiratory function. In addition to didactic instruction, before credentialing for propofol administration there should be a combination of didactic instruction and practical training. This should include an observational period during which administration under supervision of qualified instructors is conducted. Independent administration competence should be followed up through quality-improvement indicators, whose outcomes are identical to those used to assess the quality of moderate sedation and include cardiopulmonary complications, unplanned termination of procedures, emergency interventions, unplanned hospital admissions or transfers to critical care, and death.⁷

Summary Statements and Recommendations

9. Physicians targeting moderate sedation (either with an opioid/benzodiazepine combination or propofol) should be capable of rescuing a patient who enters deep sedation. Similarly, physicians targeting deep sedation require additional training with emphasis on advanced airway management and treatment of cardiorespiratory complications.
10. Training for endoscopic sedation should emphasize an understanding of medications used for endoscopic sedation and the skills necessary for the diagnosis and treatment of cardiopulmonary complications. All endoscopists should possess current certification in advanced cardiac life support (or its equivalent), and should be capable of providing respiratory support for patients with apnea and upper-airway obstruction. This includes the use of jaw thrust and chin-lift maneuvers, oral or nasal airway, and bag-mask ventilation.
11. The gastroenterology professional societies should encourage member training and certification in se-

dition, as well as continuing education and recertification.

Medicolegal Considerations

Endoscopic sedation is associated with unavoidable clinical risk, separate and apart from that associated with manipulation of the endoscope and auxiliary devices. Data for malpractice claims arising from complications of endoscopic sedation are difficult to find.¹³⁹ The Physician Insurers' Association of America database, a large malpractice claims database, does not breakdown endoscopy-related claims into those that are procedure-related and those that are sedation-related.¹⁴⁰ However, approximately 1% of all US malpractice claims involve gastroenterology, with approximately 40% of these involving procedure-related misadventures. Sedation-related complications probably account for 40%–50% of procedure-related serious adverse events.^{141,142} If the rate of malpractice claims is proportional to the rate of complications, then endoscopic sedation-related claims in the United States represent approximately 1 in every 500 malpractice claims.

Legal liability can arise from failure to administer sedation according to the standard of care or failure to obtain appropriate informed consent.^{141,143} Gastrointestinal endoscopy typically involves the collaboration of an endoscopist, 1 or more nurses/assistants, and, in about 25% of cases in the United States today, an anesthesiologist.¹ However, because the gastroenterologist bears primary duty to the patient and primary responsibility for the conduct of the procedure, he/she also may be held accountable for failure to adhere to the standard of care regarding sedation and/or failure to obtain informed consent for sedation. In fact, the endoscopist may be named as a codefendant in a lawsuit based on a sedation-related adverse event even when an anesthesiologist is administering the anesthesia.¹⁴²

In today's environment, numerous interwoven factors heighten the medicolegal relevance of sedation for gastroenterologists as follows:

1. Consumers (particularly in the United States) may expect painless medical procedures, including painless gastrointestinal (GI) endoscopy. This may incur malpractice risk related to a claim by a plaintiff of inadequate sedation.
2. Increasingly, gastroenterologists may strive for painless endoscopy, both to enhance patient compliance with screening recommendations, and/or as a practice marketing strategy. Such efforts may create additional risk of sedation-related complications.¹⁴¹
3. Many endoscopic procedures have become longer and more complex. Correspondingly, sedative drug dosing may be more complicated today than in the earlier days of GI endoscopy when sedation consisted

of small doses of a benzodiazepine and an opioid narcotic.

4. Because of political disagreements among the interested specialties, adversarial expert witnesses may be more available to testify against gastroenterologists in sedation-related liability cases.¹⁴⁴
5. In court cases involving sedation-related adverse events, endoscopists may be held to the standards applicable to anesthesiology.¹⁴¹
6. Sedation is a continuum, and all agents currently used by GI endoscopists possess the capability of causing general anesthesia.
7. Propofol, possessing different risks and benefits from traditional sedative agents such as benzodiazepines and opioids, has rapidly gained popularity within the endoscopic community. Rapid changes in established systems of practice, if not implemented cautiously, heighten the risk for adverse events.¹⁷
8. The FDA product label for propofol contains a warning that “propofol should be administered only by persons trained in the administration of general anesthesia.” In most jurisdictions, package inserts are admissible as evidence in court, so GI-directed propofol sedation presents unique medicolegal issues.¹⁴⁵
9. In many instances, sedation-related education is underrepresented in US gastroenterology professional training. Moreover, sedation-related continuing education is not commonly available to midcareer endoscopists.⁴⁵
10. Gastroenterologists underuse informed consent in general and in particular as it relates to sedation.¹⁴⁶
11. Upper GI endoscopy involves instrumentation of the head and neck, which has been associated with increased sedation-related malpractice claims.¹⁴⁷
12. Increased use of open-access endoscopy, in which the endoscopist may not have meaningful preprocedure contact with the patient, and increased procedure volumes, discourage thorough informed consent.^{1,148}

Informed Consent

The philosophic premise underlying the law of informed consent is that a patient has the right to make informed decisions about what happens to his or her body.¹⁴⁹ The determination of which procedure-related risks warrant disclosure is complex and varies by jurisdiction.^{150,151} Most states require the endoscopist to disclose any information that a reasonable physician in good standing would provide (the professional disclosure standard)¹⁵²; a minority of states apply the lay standard, by which the endoscopist must provide the information that a reasonable member of the lay public would desire. By any standard, endoscopic sedation has risks, benefits, side effects, and alternatives, and therefore warrants inclusion in the pre-endoscopy informed consent discussion.¹⁵

Informed consent for endoscopic sedation requires that the patient understand the nature of the proposed sedation, the risks and benefits associated with it, the options (including no sedation), and the risks and benefits associated with the options.¹⁵² Informed consent is not a signature on the bottom of a preprinted form, but rather “a process of communication between patient and physician”¹⁴⁹ that reduces clinical and malpractice liability risk. In malpractice litigation “the best defense a physician has is proof of complete informed consent”^{153,154} and therefore sedation-related informed consent is the endoscopists’ best defense against sedation-related liability. Conversely, “informed consent is an issue routinely included in anesthesia malpractice litigation.”¹⁵²

The current shortcomings of informed consent for endoscopy have been detailed in multiple studies and suggest strategies for achieving proper sedation-related informed consent. In a 1995 US survey, 98% of endoscopists obtained preprocedure consent, but more than one-third (38%) did not routinely discuss sedation, and 30% of the time the endoscopist was not personally involved in the informed consent discussion.¹⁴⁶ A British study suggested that roughly one quarter of patients were “inadequately informed” regarding the endoscopic procedure, despite having undergone the unit’s informed consent process.¹⁵⁵ A North American study suggested that patients in an open-access endoscopy system received “significantly less explanation” concerning the nature of the procedure than patients referred from a subspecialty clinic.¹⁴⁸ Two US endoscopy studies suggested that recall of informed consent was the same whether the consent was obtained immediately or several days before the procedure.^{156,157}

Although certain elements of the preprocedure evaluation and communication can be delegated to staff members or achieved with printed materials, most studies and experts suggest that the informed consent discussion should occur between the patient and the endoscopist.¹⁵⁸⁻¹⁶⁰ Because of education, experience, and legal responsibility the endoscopist is best qualified to disclose the risks, benefits, and alternatives to all the aspects of the procedure.¹⁶¹ A direct face-to-face informed consent discussion also provides a good opportunity for the endoscopist to assess the patient’s clinical sedation risks (eg, history of sedation reactions or difficult intubation and abnormal head and neck anatomy).¹⁶²

Other strategies that will enhance sedation-related informed consent include the use of simple language and sensitivity to language barriers and literacy limitations,^{155,160,163} preprocedure distribution of simple information leaflets provided to the patient before the procedure, and repeating explanations (eg, via leaflets mailed to the patient a week beforehand and then in a discussion the morning of the procedure). Conversely, providing information about the risks and benefits of sedation for

the first time immediately before the procedure may provide a less meaningful opportunity for the patient to process the information and therefore may lay the groundwork for a legal argument by a plaintiff that the consent was obtained under duress (“after the patient had already taken off from work, traveled to the clinic, and completed the bowel preparation, how could he/she say ‘no?’”)

Further issues related to sedation that warrant preprocedure disclosure include the following: (1) the postprocedure risks related to driving, operating heavy equipment, consuming alcohol, and exercising vigorously¹⁶⁴; (2) the possibility that the patient will not recall the procedure and postprocedure discussion; (3) the risk that despite appropriate sedation the patient will experience pain or discomfort; (4) the risk for allergic drug reactions and local reactions at the intravenous site; and (5) the risk of cardiopulmonary depression.

The gastroenterologist should provide contemporaneous documentation of the sedation-related informed consent. This can be in the form of a handwritten note or a signed, preprinted form. A 1-page form is less susceptible than a longer form to the argument by a plaintiff's attorney that the patient did not understand it. The sedation-related informed consent may be incorporated within the body of the endoscopy consent form, or it can exist as a separate document (an anesthesia-specific consent form); this second option has been advocated recently by the American Society of Anesthesiologists.¹⁶⁵

Propofol Use by the Gastroenterologist

Propofol has been used safely and effectively under the direction of endoscopists to provide sedation during endoscopy.⁶³ However, the FDA-approved product label, which states that “propofol should be administered only by persons trained in the administration of general anesthesia,”¹⁴⁵ has deterred many gastroenterologists from adopting gastroenterologist-directed propofol (GD-P), in particular because of concerns about potential liability for medical malpractice.¹ In most jurisdictions, FDA-approved product labels are admissible as evidence in court, so a jury would be allowed to weigh the off-label nature of GD-P. A product label alone generally is insufficient to establish the standard of care (the FDA does not regulate the practice of medicine), however, but would be considered by a jury alongside expert testimony. Moreover, many jurisdictions observe the respectable minority rule, which holds that there may be multiple appropriate approaches to a particular medical problem. Numerous clinical studies, professional society guidelines, and expert editorial opinion position GD-P as a respectable minority practice.¹⁶⁶ Thus, if undertaken appropriately, GD-P is medicolegally reasonable.

Maximizing patient safety and minimizing liability when administering GD-P can be accomplished by ad-

hering to 5 basic principles. First, the gastroenterologist should ensure compliance with prevailing guidelines promulgated by professional societies as well as laws and regulations imposed by medical boards and/or credentialing bodies. Second, GD-P should be limited to appropriate, relatively low-risk, patients. Third, gastroenterologists and staff should be trained in recognition and management of respiratory depression, the pharmacologic properties of propofol, and advanced cardiac life support. Fourth, endoscopy units should be equipped with resuscitation equipment and drugs, and appropriate monitoring equipment. Fifth, the informed consent discussion should inform patient of risks, benefits, and alternatives (including the option of having propofol administered by an anesthesiologist) to GD-P, and of the qualifications and experience of the endoscopist to administer GD-P.

Risk Minimization

GI society level. First, the professional GI societies should continue to develop practice guidelines regarding safe and effective sedation. Second, the professional GI societies should continue to encourage clinical research regarding best sedation practices, ideally in collaboration with other appropriate specialties. The use of a central database for adverse events such as the Clinical Outcomes Research Initiative database should be encouraged. Third, the professional GI societies should continue to encourage and develop training programs for gastroenterology fellows and practitioners regarding endoscopic sedation.

Endoscopy unit level. First, endoscopy units should adopt and encourage adherence to practice guidelines for procedure-related sedation. Second, informed consent discussion and documentation should include specific language regarding sedation. Sedation-related informed consent should follow strategies that have been shown to aid patient understanding such as the use of lay language, repetition, and the introduction of concepts well before the day of the procedure.

Endoscopist level. First, the endoscopist should personally undertake and document the informed consent discussion with the patient. Where possible, this should be witnessed by a third party. Second, the informed consent discussion and documentation should clearly include the procedure-related sedation. Third, where possible, the endoscopist should adhere to expert practice guidelines for proper administration and monitoring of procedure-related sedation. Fourth, the endoscopist should be familiar with and adhere to institutional and state laws and regulation regarding the administration of sedation. Fifth, the endoscopist should undertake continuing education in sedation. Sixth, the endoscopist should be certified in Advanced Cardiac Life Support and possess basic skills in airway intervention.

Summary Statements and Recommendations

12. Informed consent should be obtained during a face-to-face discussion between the endoscopist and the patient. During this encounter the risks, benefits, and alternatives to the proposed sedation should be reviewed and the patient should be provided with an opportunity to ask questions. The consent process should be documented.
13. The endoscopist should be ACLS certified, and provide sedation in keeping with expert practice guidelines and with institutional and state guidelines. Endoscopy units should conform to practice guidelines regarding procedure-related sedation, including documentation, training of staff, maintenance of rescue equipment, creation of appropriate emergency protocols, and quality assurance programs.
14. Gastroenterologist-directed propofol sedation is medicolegally reasonable, but requires appropriate endoscopist training, patient selection, and adherence to protocols for administration, as well as compliance with institutional and local regulations.

Future Directions in Endoscopic Sedation

The benzodiazepines and opioid narcotics are the drug classes most widely used for endoscopic sedation within the United States.¹ Although these agents produce effective sedation and analgesia for most patients, they lack the pharmacologic properties necessary to achieve optimal sedation during an endoscopic procedure. For example, the opioid analgesics are associated with troublesome side effects such as respiratory depression, bradycardia, nausea, and vomiting. Further, both fentanyl and meperidine, the 2 most widely used opioids, are relatively long acting and their residual effects may be experienced for several hours after completion of an endoscopy. Similarly, the hypnotic effects of the benzodiazepines may persist for 4–6 hours. Midazolam, the first water-soluble benzodiazepine, has several benefits over diazepam including a shorter duration of effect and the elimination of pain on intravenous injection.²⁹ Benzodiazepines, similar to opioids, also may produce respiratory depression and hypotension and their co-administration enhances the potential for these complications.²³ Consequently, whether alone or in combination, the opioids and benzodiazepines lack the pharmacokinetic and safety profile required for optimal sedation and analgesia during an endoscopic procedure.

The ideal agent for endoscopic sedation should possess sedative, analgesic, and amnestic properties and a pharmacokinetic profile compatible with rapid onset (1–2 min), brief duration (5–10 min), and fast recovery (15–20 min). It also should provide a predictable pharmacodynamic response within the range of moderate sedation, exert minimal depressant effects on the cardiopulmonary

system, and possess a pharmacologic antagonist. Finally, its use by an endoscopist and/or nurse should comply with state and federal regulations, and it must be cost effective compared with current methods of sedation.

Efforts to improve endoscopic sedation include the evaluation of new drugs and the re-assessment of existing ones, as well as the development of new methods of drug delivery. This section will examine several of the most promising prospects for the future.

Fospropofol Disodium

Fospropofol disodium, a water-soluble prodrug of propofol, is an investigational agent designed to modify the pharmacokinetic properties of propofol emulsion in order to enhance its effectiveness and safety profile during procedural sedation. Fospropofol is hydrolyzed rapidly by alkaline phosphatases, releasing propofol as an active metabolite along with formaldehyde and phosphate.^{167,168} The formaldehyde is converted rapidly to formate. After bolus administration of fospropofol, the plasma concentration of liberated propofol has a slower upward slope, a lower peak, and a more extended plateau phase when compared with an equipotent dose of propofol emulsion.

A phase 2, double-blind, multicenter, dose-response study randomized patients undergoing elective colonoscopy to 1 of 4 weight-based doses of fospropofol disodium (2, 5, 6.5, or 8 mg/kg) or midazolam (.02 mg/kg).¹⁶⁹ All patients received a pretreatment dose of fentanyl (50 μ g). Sedation success, the primary study end point, was dose-dependent with the 6.5- and 8-mg/kg doses achieving significantly better sedation outcomes than 2 mg/kg. Similar trends were observed for other study parameters such as time to sedation, requirements for supplemental doses of sedation and/or fentanyl, and the use of alternative sedation. Fospropofol 6.5 mg/kg produced moderate sedation throughout most of the examination (84.6%), and only 1 of 26 patients in this dose group experienced transient deep sedation. More than 90% of patients and physicians indicated their satisfaction with this level of sedation. The time from completion of the procedure until the patient was ready to be discharged was 9.1 minutes. The most common adverse events were burning sensation (23.8%), paresthesia (8.9%), and pruritus (7.9%), and there were no serious adverse events. Clinical trials evaluating fospropofol disodium for colonoscopy, bronchoscopy, and minor surgical procedures are currently in progress.

Patient-Controlled Analgesia/Sedation

Patient-controlled drug delivery enables the patient to control the timing of medication administration. Colonoscopy, characterized by brief periods of intense pain related to stretching or distension of the colon wall, would appear to be ideally suited to patient-controlled analgesia/sedation (PCA/S).

PCA/S is accomplished with a specialized pump that delivers a preset amount of medication in response to the press of a button. A lockout time often is used to prevent the delivery of additional doses until the previous one has achieved peak effect. An initial bolus dose and a background continuous infusion also can be programmed into the system. For a drug to be effective in a patient-controlled delivery system, it should have rapid-on and rapid-off pharmacokinetic properties. Propofol, either alone or combined with an opioid narcotic, is the drug used most often for PCA/S.

Multiple trials have shown that PCA/S is safe and effective for endoscopic sedation.¹⁷⁰⁻¹⁷⁶ Roseveare et al¹⁷¹ described patient-controlled sedation using propofol/alfentanil (mean doses, 98 mg/120 μ g) in 16 patients undergoing colonoscopy. Recovery time was 9 minutes, patients were satisfied with the degree of sedation and comfort achieved, and there were no significant adverse events. In a second study, the same investigators compared PCA/S with conventional sedation using pethidine and diazepam (mean doses, 50 and 15 mg, respectively) in 66 patients undergoing colonoscopy. The patients receiving PCA/S were sedated more lightly, experienced slightly more pain during the examination, and recovered more quickly. Patients in both treatment arms were satisfied with the sedation.

Lee et al¹⁷² randomized 100 elderly patients undergoing colonoscopy to either patient-controlled sedation or intravenous sedation. The patient-controlled group received a mixture of propofol and alfentanil, whereas the intravenous group received meperidine and diazepam (mean doses, 30.1 and 5.8 mg, respectively). Both treatment groups were satisfied with the sedation and analgesia, although there was a trend toward more discomfort in the patient-controlled group. Heuss et al¹⁷⁴ compared propofol delivery by PCA/S vs bolus administration (mean propofol doses, 124.2 and 141.6 mg, respectively). Patient satisfaction and safety parameters were similar in the 2 treatment groups. More than a third of all screened patients declined to participate in the study, indicating a desire either to be asleep during the procedure (20%) or an unwillingness to assume responsibility for sedation (73%).

On the basis of published studies, several conclusions about PCA/S and endoscopy can be drawn. First, patients receiving PCA/S experience procedure-related satisfaction that is at least comparable with, and in some cases better than, conventional sedation. Second, recovery is faster with PCA/S because the total drug dosage usually is reduced. Third, PCA/S may not be suitable for all persons because it requires both the willingness and capacity to comply with instructions. Several patient characteristics have been shown to predict poor tolerance for PCA/S, including young age, female sex, and increased preprocedural anxiety.

Target-Controlled Infusion

A target-controlled infusion (TCI) system is designed to deliver an intravenous drug using an infusion pump and a computer.¹⁷⁷ The computer, programmed with a drug-specific, population-based pharmacokinetic model, calculates the infusion rate that is necessary to achieve the target or desired drug concentration in the blood. The computer signals the infusion pump to deliver the amount of drug necessary to achieve the predetermined drug concentration. In contrast to PCA/S, which provides a constant-rate infusion and may lead to accumulation and increasing drug concentration, TCI uses a mathematic model to calculate the initial dosage needed to achieve a desired concentration of drug, and then makes appropriate adjustments in the rate of infusion to maintain that level. The pharmacokinetic model adjusts for a variety of patient characteristics that may affect drug disposition such as age, sex, body weight, and comorbid disease. Individual responses to a given drug concentration will differ as a result of pharmacodynamic variability. Consequently, the patient must be monitored continuously and adjustments made as necessary to the target concentration. This method of TCI, designed to deliver a target concentration of drug that has been selected by a physician, is referred to as *open-loop* because there is no feedback from the patient.

In contrast, a *closed-loop* system uses feedback from a real-time measure of drug effect such as muscle relaxation, auditory evoked potential, or another measure of sedation to regulate the concentration of delivered drug. The operator selects the desired level of drug effect, and the computer regulates the infusion pump to achieve and maintain that set-point. The BIS, reflecting the level of consciousness, is the response that has been studied most extensively for this application.^{128,129} Theoretically, a closed-loop system should provide sedation that is more individualized than an open-loop system, reducing the potential for undersedation and oversedation.

The use of TCI, both open- and closed-loop systems, has been studied during endoscopy. Fanti et al¹⁷⁸ assessed 205 patients undergoing endoscopic retrograde cholangiopancreatography using TCI of propofol. An initial plasma concentration of 4 μ g/mL was targeted, and the dose subsequently was titrated between 2 and 5 μ g/mL by an anesthesiologist to maintain patient cooperation and comfort. A single bolus of fentanyl (50–100 μ g) was provided if patients showed signs of inadequate analgesia. The quality of sedation was considered excellent in 201 of 205 patients by both the endoscopist and the nurse. Four patients developed hypoxia, including 1 patient who required manual ventilation.

Gillham et al¹⁷⁹ studied 20 patients undergoing endoscopic retrograde cholangiopancreatography who received TCI of propofol combined with a patient-controlled handset. An initial propofol plasma concentration

of 1.0 $\mu\text{g}/\text{mL}$ was selected, with increases of 0.2 $\mu\text{g}/\text{mL}$ after each trigger of the handset, to a maximal target concentration of 3.0 $\mu\text{g}/\text{mL}$. Sixteen of 20 patients completed the procedure successfully with this sedation system, although 4 were considered to be oversedated. The system was considered a failure in an additional 4 patients, including 3 who were undersedated. In another trial, Campbell et al¹⁸⁰ evaluated TCI of propofol in conjunction with a patient-controlled handset in 20 patients undergoing colonoscopy. The initial target plasma concentration of propofol was 1.0 $\mu\text{g}/\text{mL}$, and patients could make .2- $\mu\text{g}/\text{mL}$ increments with each press of the trigger, to a maximum of 4.5 $\mu\text{g}/\text{mL}$. Seven patients required a manual override of the system by the investigator, 3 to increase sedation and 4 because of oversedation.

Leslie et al¹⁸¹ studied 16 patients sedated with TCI of propofol using a closed-loop system guided by the BIS. The median propofol concentration was 2.3 $\mu\text{g}/\text{mL}$ using a BIS set-point of 80. No patient became hemodynamically unstable or required airway support, and patient and physician satisfaction were high. Stonell et al¹⁸² compared TCI of propofol with anesthesiologist-administered propofol in a study of 40 patients undergoing colonoscopy. The initial target plasma concentration of propofol was set at .8 $\mu\text{g}/\text{mL}$, with increments of 0.1 $\mu\text{g}/\text{mL}$ triggered by a patient-control handset. Patients in the TCI group were sedated more slowly (13 vs 3 min, $P < .0001$), less deeply, and received a lower total dose of propofol (238 vs 288 mg, $P = .51$) than the anesthesiologist-administered propofol group. Patient satisfaction and recovery times were comparable in the 2 groups.

Computer-Assisted Personalized Sedation

Computer-assisted personalized sedation is an investigational device that combines TCI of propofol, a unique feedback system based on patient response to audible and tactile stimuli, and a physiologic monitoring unit.¹⁸³ The device is programmed to reduce or stop an infusion in response to either a clinical (unresponsiveness to audible/tactile stimuli) or physiologic (oxygen desaturation, hypoventilation) indication of oversedation. When patient responsiveness has returned and the physiologic parameters have been restored to normal, drug delivery is resumed at a reduced maintenance rate, based on a recalculated dosing algorithm. Computer-assisted personalized sedation is designed to deliver propofol safely and effectively by a trained physician/nurse team.

The feasibility of computer-assisted personalized sedation was evaluated recently by US and Belgium investigators in 2 studies using an identical protocol. A total of 96 patients underwent endoscopy with computer-assisted personalized sedation (colonoscopy, 48; EGD, 48).¹⁸⁴ All subjects received a pre-induction dose of fentanyl (25–100 μg), followed 3 minutes later by an infusion of propofol. The total dose and range of propofol

dosing in the US and Belgium studies was 70.4 mg (20–130 mg) and 76.7 mg (20–350 mg), respectively. There were a total of 8 episodes of transient oxygen desaturation ($\text{S}_a\text{O}_2 < 90\%$) lasting 16–56 seconds, and 73 episodes of transient apnea lasting 1–37 seconds. Patients remained moderately sedated throughout the examination. Recovery time, defined by an Aldrete score of 12 or higher, was less than 1 minute for the majority of patients. There were no serious drug- or device-related events, and intervention by an anesthesiologist was not required. The majority of study subjects had little or no recall of the endoscopic procedure, and satisfaction ratings by physicians and patients were excellent. Preliminary data from these 2 studies suggest that computer-assisted personalized sedation may provide endoscopists with the ability to deliver propofol safely and effectively without the assistance of an anesthesia professional. A large, multicenter pivotal trial is currently in progress.

Summary Statements and Recommendations

15. Although the majority of patients having upper and lower endoscopy can be sedated satisfactorily using an opioid/benzodiazepine combination, the pharmacologic properties of these agents render them suboptimal for brief, ambulatory endoscopic procedures. The increase in propofol use for endoscopic sedation during the past few years indicates that improved methods of sedation are needed.
16. New drugs and drug-delivery systems for endoscopic sedation, including fospropofol disodium, patient-controlled sedation, TCI, and computer-assisted personalized sedation currently are being evaluated for effectiveness and safety. Randomized, controlled studies will be required to compare these new methods with present practices. In addition to the standard assessment of efficacy and safety, functional recovery (when can the patient resume normal activity/work), patient and physician satisfaction, staffing requirements, and the economic impact of these new methods of sedation should be compared with conventional modes of treatment.

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