

New Options for Endoscopic Sedation

a report by

Lawrence B Cohen, MD

Associate Clinical Professor, The Mount Sinai School of Medicine, New York

Analgesia and sedation are considered by most endoscopists and patients to be essential elements of the endoscopic procedure. While intended primarily to relax and improve patient comfort, sedation also reduces the patient's risk of physical injury and improves the efficiency and outcome of endoscopy.

Intravenous sedation is standard practice during endoscopic procedures performed in the US.¹ A nationwide survey in 2004 indicated that nearly 99% of endoscopists use sedation routinely during endoscopy. This finding is consistent with the results of a recent study by Subramanian, indicating that patients undergoing colonoscopy are most concerned about not experiencing pain during an examination and awakening promptly upon completion of the procedure. A small minority of patients, primarily men with graduate educations, may be more willing to consider undergoing an unsedated procedure.² Sedation practices are remarkably similar throughout most of Western Europe, based on the results of the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) study³ as well as nationwide surveys of sedation practice within Great Britain,⁴ Spain,⁵ and Finland,⁶ which suggest that sedation is the majority practice in 75 and 90% of esophagogastroduodenoscopies (EGDs) and colonoscopies, respectively, in Western European nations.

The drugs used traditionally for endoscopic sedation are the opioids and benzodiazepines, administered either alone or in combination. While three-quarters of endoscopists in the US continue to use an opioid combined with a benzodiazepine, the preferred agent within each class has changed during the past 15 years. Midazolam is now the preferred benzodiazepine, rather than diazepam, due to its shorter duration of effect and improved safety profile. Fentanyl and meperidine are the two most widely used opioids, with fentanyl being preferred among younger endoscopists. The remaining quarter of endoscopists in the survey use propofol-based sedation, usually administered by an anesthesia specialist.¹

This article reviews the sedation agents used in routine practice across the US, including their strengths and weaknesses, and presents new agents and techniques that may improve the clinical practice of endoscopic sedation.

Established Sedation Regimens

Moderate sedation, previously referred to as conscious sedation, is a drug-induced depression of consciousness during which a patient is capable of responding purposefully to verbal commands with or without light tactile stimulation.⁷ Moderate sedation is usually adequate for controlling the pain and discomfort of endoscopic procedures, although some patients will either require or expect a deeper level of sedation. As the depth of sedation increases from moderate to deep, so too does the risk of a cardiopulmonary

complication. Respiratory complications, either central hypoventilation or upper airway obstruction, are the most frequent issues likely to require some form of intervention.⁸ While it is not always possible to achieve the targeted level of sedation—some patients may become more deeply sedated than desired—the goal of moderate sedation provides the best balance between safety and effectiveness.

Narcotics and Benzodiazepines

Opioids and benzodiazepines are used for the relief of pain and anxiety, respectively. When used alone, the incidence of respiratory complications with either midazolam or fentanyl is quite low. In contrast, the rate of complications increases several-fold when both drugs are given in combination. It should be emphasized that both the pharmacological effects and the side effects of benzodiazepines and opioids are synergistic, so these drugs must be used with caution.⁹ Within the US, most of the state Boards of Nursing permit registered nurses to administer benzodiazepines and opioids, provided that the target is moderate sedation.

Irrespective of which agents are being administered, drug dosing should always be titrated to clinical and physiological effect. An initial bolus size is selected based on knowledge of the patient (age, weight, comorbid illnesses, and sedation history) and the pharmacodynamic properties of the drug(s). Subsequent boluses are given at time intervals based on the pharmacokinetic profile of the drugs. This requires an understanding of time to peak effect, duration of effect, and drug–drug interaction. It is important to appreciate that there is tremendous pharmacodynamic variability between subjects, meaning that the concentration–effect relationship may differ widely from one person to another. The reasons for such inherent differences in drug response between subjects relates to genetic factors as well as organ function, concurrent medications, and underlying disease. This pharmacodynamic variability in response to opioids and benzodiazepines can be three- to five-fold.¹⁰

The use of benzodiazepines and opioids provides several important benefits, including a long history of safety, efficacy, and widespread acceptance by non-anesthesiologists.¹¹ Additionally, the existence of a pharmacological antagonist for benzodiazepines and opioids is believed to provide these drugs with an added level of safety compared with other drug classes. Nonetheless, the benzodiazepines and opioids have important drawbacks. First, a small proportion of patients—estimated at 5–15%—are inadequately sedated with these drugs.¹² This subgroup of patients, sometimes described as ‘hard-to-sedate’ patients, includes those with a history of chronic alcohol or drug abuse, chronic users of opioid narcotics or sedative hypnotic agents, and the morbidly obese. Second, the induction of sedation with opioids and benzodiazepines averages six to 12 minutes, and

full recovery from these agents may take 24 hours or more. In some instances, patients may miss work the day after a procedure due to the extended effects of sedation.¹³ When one considers that the average colonoscopy requires 20 minutes to complete, the ideal sedation agent should possess duration of effect between five and 10 minutes so that recovery and discharge may be completed within 15–20 minutes.

Propofol

Propofol is formulated in a lipid-based oil emulsion that contains soybean oil, egg lecithin, and glycerol and is supplied in 20, 50, and 100ml vials. It is a pure sedative/anesthetic that works by binding to the β -subunit of the gamma-amino butyric acid-A (GABA_A) receptor, leading to hyperpolarization due to increased channel opening time. Propofol was approved by the US Food and Drug Administration (FDA) in 1989 for the induction and maintenance of anesthesia.

Propofol has a very quick onset of action (30–45 seconds) and undergoes rapid metabolism. Propofol must therefore be administered frequently to maintain sedation levels, particularly when used as a single agent. Non-anesthesiologists can be trained to safely administer propofol for endoscopy, although it should be emphasized that its pharmacological properties are quite different from those of the opioids and benzodiazepines. Experience with these drugs is not sufficient training to qualify someone to administer propofol. Persons planning to introduce a propofol sedation program within their endoscopy suite should also investigate applicable accrediting standards, state nursing board and local institutional policies.¹³

The term 'gastroenterologist-directed propofol' (GDP) is intended to distinguish propofol administration under the guidance of a gastroenterologist from propofol use under the care of an anesthesia provider (also referred to as monitored anesthesia care, or MAC). Two dominant methods of GDP have been studied in clinical practice: nurse-administered propofol sedation (NAPS) and balanced propofol sedation. Developed by John Walker, MD, NAPS utilizes specially trained registered nurses whose sole responsibilities are patient monitoring and the administration of propofol.¹⁵ In most case series of NAPS, propofol is given as a single agent and deep sedation is targeted. Several notable exceptions to this exist, however, including the Swiss and Japanese, who have reported their experience with significantly reduced doses of propofol targeted to moderate sedation.^{16,17} NAPS has been used successfully in community-based ambulatory endoscopy centers as well as in academic settings, with high levels of patient satisfaction, rapid post-procedure recovery and discharge, and an outstanding safety record.

Unlike NAPS, balanced propofol sedation combines propofol with small induction doses of fentanyl (50–75mcg) and midazolam (0.5–1.0mg). Propofol is then administered in small titrated doses of 5–15mg until moderate sedation is achieved. The dose of propofol used for maintenance is 25% of the induction dose (to a maximum of 15mg). For example, if the induction dose of propofol was 50mg, the maintenance dose of propofol will be 10mg.

The co-administration of propofol with one or more additional agents reduces the total dose of propofol required, improves sedation and analgesia, and potentially adds an element of reversibility to the sedative regimen.^{18,19} Midazolam can potentiate the action of propofol, reducing the dosage requirement by as much as 44%. Van Natta randomized patients

undergoing routine colonoscopy to one of four treatment arms: propofol; propofol and fentanyl; propofol and midazolam; or propofol, midazolam, and fentanyl.²⁰ While the time required for sedation initiation was nearly identical in all treatment groups, the mean dose of propofol required to complete the examination was reduced by 35, 42, and 62% in the fentanyl, midazolam, and fentanyl/midazolam arms, respectively. Furthermore, patients sedated with propofol and one or more additional agents remained moderately sedated throughout the examination, in contrast to patients receiving propofol alone, who were deeply sedated. These findings have been re-confirmed in several large clinical studies.^{18,21}

Prospective studies have shown that propofol use is associated with a statistically significant improvement in comfort and sedation score compared with midazolam and meperidine.²² Serious adverse events that have been associated with propofol include severe respiratory depression, hypotension, and bradycardia, but it is rare that these require intervention.²³ Consequently, guidelines published by the American Gastroenterological Association Institute indicate that GDP sedation is "medicolegally reasonable, but requires appropriate endoscopist training, patient selection, and adherence to protocols for administration."¹⁴

Another option for endoscopic sedation is patient-controlled sedation. In most reports, propofol has been used, either alone or combined with alfentanil, a short-acting opioid. The benefits of patient-controlled sedation include faster recovery times.^{24–26} At present, only small studies have been reported and it remains to be determined in large-scale clinical trials whether patient-controlled sedation is feasible and well-tolerated.

Thus, there is a need for an agent that works like propofol but that can be more readily, reliably, and safely titrated to patients. The ideal sedation agent should have quick onset and short duration of action, permitting rapid induction of sedation and fast recovery of function. It should also produce sedation and anterograde amnesia in order to ensure a satisfactory patient outcome. The drug must also possess a safety profile that is at least equivalent to, if not better than, the medications currently in use.

Fospropofol—A New Agent in Development

Fospropofol disodium (MGI Pharma, Inc, Bloomington, MN, a wholly owned subsidiary of Eisai Corporation of North America) is a water-soluble prodrug of propofol that is rapidly hydrolyzed by alkaline phosphatases, releasing propofol, phosphate, and formaldehyde (rapidly converted to formate). These inactive metabolites do not accumulate above endogenous levels.²⁷ Fospropofol has undergone clinical evaluation for sedation in a variety of diagnostic and therapeutic settings.

Fospropofol is rapidly and completely metabolized to propofol *in vitro*, but differs from propofol with respect to its pharmacokinetic and pharmacodynamic properties in a way that might enhance its effectiveness and safety profile during procedural sedation. Following intravenous administration of fospropofol, there is a smooth and predictable rise in the plasma concentration of fospropofol-derived propofol. Also, fospropofol produces a lower maximum propofol concentration than bolus or rapid infusional administration of the lipid emulsion formulation of propofol.²⁸ The early elimination kinetics of fospropofol-derived propofol are slower than those of propofol from the lipid-emulsion formulation; however, the terminal elimination kinetics are the same.

Fospropofol has undergone evaluation as a sedative agent for diagnostic and therapeutic procedures, including upper and lower gastrointestinal endoscopy, bronchoscopy, interventional cardiac procedures, and a variety of brief surgical procedures. In this discussion, however, I will limit my remarks to studies involving colonoscopy. Two pivotal studies provide important data on the future role of fospropofol. The first of these was a phase II dose-ranging trial that assessed the efficacy and safety of four fospropofol doses (2.0, 5.0, 6.5, and 8.0mg/kg). A fifth treatment arm received midazolam 0.02mg/kg and served as safety reference. All patients received fentanyl five minutes prior to administration of the initial dose of sedative medication.²⁹ The results of this trial showed a dose-dependent sedation effect across the fospropofol dosing groups, with the 6.5 and 8.0mg/kg groups producing superior sedation (69 and 96%, respectively; $p < 0.05$). On average, full recovery required nine minutes. As expected, more episodes of deep sedation were observed with 8.0mg/kg versus the 6.5mg/kg group (25 and 4%, respectively), although no serious sedation-related adverse events were observed in any treatment arm. From the standpoint of safety, fospropofol 6.5mg/kg was well tolerated, and was not associated with any serious cardiopulmonary adverse events. Consequently, a decision was made to go forward with the 6.5mg/kg bolus dose in the phase III clinical trial.

The efficacy and safety of fospropofol 6.5mg/kg were confirmed in the randomized, double-blind, multicenter phase III trial. Sedation success was achieved in 87% of 314 patients receiving 6.5mg/kg compared with 26% of patients receiving a subtherapeutic dose of fospropofol (2mg/kg). Colonoscopy was initiated after ≤ 2 supplemental doses in 76% of patients in the fospropofol 6.5mg/kg group compared with 12% of the subtherapeutic group. In terms of depth of sedation, the 6.5mg/kg group

spent fractionally more of their time in deep sedation than the subtherapeutic dose group (0.9 and 0%, respectively), although it took only half the time to reach sedation in the former group. Times taken to reach full alertness post-procedure and to discharge thereafter were comparable.³⁰ Patient and physician satisfaction with fospropofol were exceptional: 96% of patients in the 6.5mg/kg group expressed a willingness to use the sedative again. Patient satisfaction with the overall procedure and comfort levels were 9.4 and 9.1 out of 10, respectively, in the 6.5mg/kg group, versus a still respectable 9.1 and 8.7, respectively, in the subtherapeutic group. Physicians also reported higher satisfaction levels with the higher dosage. However, 100% of patients who had the lower dose remembered being awake during the procedure, versus 51% in the higher treatment group.

There were no major or serious treatment-related adverse events. The most frequently reported side effects of fospropofol were transient paresthesias and pruritus. In summary, the fospropofol 6.5mg/kg dosing regimen is associated with predictable levels of moderate sedation, a high level of sedation success, and patient and physician satisfaction.

Summary and Conclusions

Sedation is commonly used for patients undergoing an endoscopic procedure. Sedation is designed to improve patient satisfaction, increase compliance with colorectal screening guidelines, and improve the safety and accuracy of the examination. The standard sedation agents—benzodiazepines and opioids—have been demonstrated to be safe and effective, although their pharmacological properties are not ideally suited for brief ambulatory procedures. New sedative agents in clinical development that deliver propofol in a predictable and controlled manner, such as fospropofol, have the potential to fulfill an unmet need. ■

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