



## Sedation and analgesia in gastrointestinal endoscopy: What's new?

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### Abstract

Various types of sedation and analgesia technique have been used during gastrointestinal endoscopy procedures. The best methods for analgesia and sedation during gastrointestinal endoscopy are still debated. Providing an adequate regimen of sedation/analgesia might be considered an art, influencing several aspects of endoscopic procedures: the quality of the examination, the patient's cooperation and the patient's and physician's satisfaction with the sedation. The properties of a model sedative agent for endoscopy would include rapid onset and offset of action, analgesic and anxiolytic effects, ease of titration to desired level of sedation, rapid recovery and an excellent safety profile. Therefore there is an impulse for development of new approaches to endoscopic sedation. This article provides an update on the methods of sedation today available and future directions in endoscopic sedation.

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### INTRODUCTION

The best methods for analgesia and sedation during gastrointestinal endoscopy are still debated. Providing an adequate regimen of sedation/analgesia might be considered an art, influencing several aspects of endoscopic procedures: the quality of the examination, the patient's cooperation and the patient's and physician's satisfaction with the sedation<sup>[1]</sup>.

Ensuring adequate sedation and analgesia and the patient's clinical stability by appropriate monitoring during endoscopic procedures has become extremely important over the last 10 years or so<sup>[2,3]</sup>. Open-access endoscopy, where no outpatient evaluation is required before the procedure, is increasingly common. Patients, sometimes with comorbidities, arrive for screening or routine endoscopy without having been assessed for pathologies that might influence procedural sedation. In addition, in situations where the examination is more invasive or time-consuming, the level of sedation must be optimized in order to achieve ideal procedural conditions.

The best sedation strategy should be tailored to the individual patient, based on the clinical risk evaluation and the type of procedure to be done<sup>[3-5]</sup>. Sedation can be defined as a drug-induced depression in the level of consciousness. Sedation and analgesia comprise a continuum

of states ranging from minimal sedation (anxiolysis) through general anesthesia. The majority of endoscopic procedures are done under a regimen of moderate sedation and the literature suggests that combining a benzodiazepine with an opioid provides an effective level of sedation. Targeting a moderate level of sedation gives a better overall profile than a deeper level and should also give a better safety margin for a non-anesthesiologist<sup>[3]</sup>. However, Patel *et al.*<sup>[6]</sup>, measuring sedation levels during endoscopic procedures performed with a combination of meperidine and midazolam, observed that unintended excursion into a deeper level of sedation did not generally result in adverse outcomes and suggest the safety margin is wide around targeted moderate sedation.

An important general principle about achieving moderate sedation with a combination of drugs is that the combined effect of an opiate and benzodiazepine is much greater than the additive effects of the single drugs so there is a greater risk of complications<sup>[7]</sup>.

The target level of sedation and the agents chosen will depend on the characteristics of the endoscopic procedure (length and painfulness), individual patient's factors (age, comorbidities, anxiety, *etc.*), patient's preferences, and the need for cooperation<sup>[8]</sup>. A critical point for the non-anesthesiologist is that although a patient's characteristics help establish the target dosage, it is impossible to predict accurately the exact dose needed to complete the procedure. Even when the blood levels of a particular drug are similar, one patient's experience of sedation can be quite different from that of another. Therefore, a successful outcome is dependent on an understanding of incremental dosing, the synergistic effects of drug classes, and the onset of action and peak effects of sedation agents. In addition, clinicians must always be prepared to rescue patients who move to the next deeper level of sedation<sup>[7]</sup>.

Propofol is a short-acting intravenous agent with a rapid onset of action, short recovery profile, anti-emetic properties and good amnesic effects. Several studies have suggested that propofol offers significant advantages over benzodiazepines and opioids for sedation during endoscopic procedures and two large prospective studies indicated it was more effective and safer than midazolam and meperidine for reaching and maintaining an adequate level of sedation during endoscopic procedures, resulting in better titration of the level of sedation, and shorter recovery times<sup>[9-14]</sup>.

In 2004 the American College of Gastroenterology, American Gastroenterology Association and the American Society for Gastrointestinal Endoscopy issued a joint statement affirming that large case studies indicate that adequately trained nurses, supervised by a physician, can safely and effectively administer propofol. Worldwide experience with gastroenterologist-directed sedation with propofol combined with improvements in our understanding of its dosing and titration for moderate sedation, as stated by Cohen *et al.*<sup>[15]</sup>, have prompted several medical societies to question the real necessity of restricting its use to anesthesiologists. In 2004 the American Society for Gastrointestinal Endoscopy, in its Training Guidelines for Use of Propofol

in Gastrointestinal Endoscopy, stated: "While properly trained physicians can administer propofol, regulations governing its administration by non-physician personnel are variable on a state-by-state basis"<sup>[4,15]</sup>. Nevertheless, in April 2004 the American Society of Anesthesiologists (ASA) recommended that, when propofol is used for moderate sedation and analgesia, it should be administered by someone trained in administering general anesthesia. This is in line with the "black box" warning for propofol, in which the manufacturer makes the same recommendations. Furthermore, in 2005 the ASA stated that: "Propofol is an anesthetic drug and the ASA believes that the involvement of an anesthesiologist in the care of every patient undergoing anesthesia is optimal"<sup>[16]</sup>.

In a recent update article Rex *et al.*<sup>[17]</sup> opined that given the big financial incentives from special interest groups, such as the anesthesiologists' community, it is unlikely that non-anesthesiologist-directed propofol administration will expand dramatically in the near future.

## NON-ANESTHESIOLOGIST PROPOFOL SEDATION

Many studies address the safe and effective administration of propofol during gastrointestinal endoscopy, by either physicians or trained nurses. In 2005 the cumulative reported experience with nonanesthesiologists-administered propofol during gastrointestinal endoscopic procedures was more than 80 000 patients<sup>[18-26]</sup>. In these reports there were no patients requiring endotracheal intubation or resulting in death. In 2005, in a large prospective trial involving three endoscopy units (Indiana, Oregon and Switzerland) and 36 743 cases of nurse-administered propofol sedation, the authors concluded: "Trained nurses and endoscopists can administer propofol safely for endoscopic procedures. Nurse-administered propofol sedation is one potential solution to the high cost associated with anesthesiologist-delivered sedation for endoscopy" and moreover: "It remains uncertain whether large prospective series of NAPS with safe performance will satisfy the concerns of anesthesia societies regarding the safety of propofol administration for endoscopy by appropriately trained registered nurse/endoscopy teams"<sup>[25]</sup>.

In 2007 Cohen and the AGA Institute, reviewed the standard practice of endoscopic sedation and, regarding the use of gastroenterologist-directed propofol, recommended that: (1) 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 regulation; and (2) 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 programme<sup>[15]</sup>.

In 2008 Rex, in an update about gastroenterologist-directed propofol, summarized published literature on the safety of gastroenterologist-directed propofol reporting more than 220 000 cases without a single reported death. In only 1 case endotracheal intubation was required during endoscopic retrograde cholangiopancreatography (ERCP) with full patient's recovery. As stated by Rex, despite evidence that there are large case series supporting the use of propofol sedation by non-anesthesiologists, numerous obstacles have persisted regarding its expansion; most prominent of these is the institutional control that anesthesiologists maintain over sedation policies<sup>[17]</sup>. The ASA Task Force recommends that patients receiving propofol should receive care consistent with deep sedation and that those personnel should be capable of rescuing the patient from general anesthesia<sup>[2]</sup>. However, there is abundant evidence that propofol can be administered safely by non-anesthesiologists.

In a recent paper by Rex *et al.*<sup>[26]</sup>, a world-wide multicenter safety review of 646 080 (223 656 published and 422 424 unpublished) endoscopist-directed propofol sedation cases was conducted. Endotracheal intubation, permanent neurologic injuries and deaths were 11, 0 and 4, respectively. The 4 deaths occurred in patients with significant comorbid illness. In this series endoscopist-directed administration of propofol appears to have a lower mortality rate than that in published data on traditional sedation with benzodiazepines and opioids and a comparable rate to that on general anesthesia by anesthesiologists.

The Endoscopic Section of the German Society for Digestive and metabolic Diseases have recently published the Guideline for Sedation for Gastrointestinal Endoscopy 2008. This guideline states: "For simple endoscopic examinations and in low-risk patients, sedation (with propofol) should be induced by a properly qualified physician and can then be monitored by an experienced person with appropriate training. The person must not have any other tasks while monitoring the sedation. Propofol may be administered by a properly trained and experienced person who has this as his or her sole task (recommendation grade A, strong consensus)"<sup>[28]</sup>. Furthermore, the literature findings on the safety of endoscopist-administered show that the use of an anesthesiologist for sedation for endoscopic procedures is costly. The recommendation of the German guideline is still that calling in an anesthesiologist should be considered only for patients with a high risk profile such as high ASA grade (III-IV), or pathological and anatomical features associated with a higher risk of airway obstruction during the intervention.

Recently, the American Association for the Study of Liver Disease, American College of Gastroenterology, American Gastroenterological Association and American Society for Gastrointestinal Endoscopy have released the "Position statement: nonanesthesiologists administration of propofol for GI endoscopy" published in 2009 December, which concludes that the administration by non-anesthesiologists of propofol *vs* standard sedation with benzodiazepines and opioids is comparable with respect to their efficacy and safety profile<sup>[29]</sup>.

Proper training and patient selection are mandatory for the safe practice of nonanesthesiologists-administered propofol sedation.

The Sedation Task Force, which was chaired by Cohen LB and included representatives from each of the four societies, was convened to develop a document designed to provide an evidence-based assessment of propofol-mediated sedation by properly trained nonanesthesiologists. The document was approved by the governing boards of all four societies.

A number of recommendations are made in the statement regarding non anesthesiologist propofol sedation (NAPS): (1) The safety profile of NAPS is equivalent to that of "standard sedation" with respect to the risks of hypoxemia, hypotension and bradycardia for upper and lower endoscopy, ERCP and endoscopic ultrasound (EUS). The worldwide experience with NAPS during EUS and ERCP, however, is insufficient to draw definitive conclusions about its use in these settings; (2) For upper and lower endoscopy, ERCP and EUS, the time for sedation induction and the recovery time using NAPS are shorter in comparison to that with standard sedation; patient satisfaction is equivalent or slightly superior; and (3) For ERCP and EUS, NAPS is more cost-effective than standard sedation. The use of anesthesiologist-administered sedation for healthy, low-risk patients undergoing routine gastrointestinal endoscopy results in higher costs with no proven benefit with respect to patient safety or procedural efficacy.

NAPS requires the acquisition of skills and abilities that are distinct from those necessary for standard sedation. Training programs that are both didactic and practical should be provided by Scientific Societies.

Although current methods of sedation are effective for the majority of patients undergoing endoscopy, techniques that enhance patient satisfaction, safety and recovery are desirable.

Infusion platforms that permit control of drug delivery by the patient are promising alternatives to current methods of sedation.

## PROPOFOL INFUSION PLATFORMS

New concepts in endoscopic sedation include enhanced mechanisms for drug delivery such as target-controlled infusion (TCI) and patient-controlled sedation or analgesia (PCS or PCA). The TCI pump, first described in the 1980s, provides infusions based on pharmacokinetic models of the specific drug, using a computer-controlled pump; the target concentration (in µg/mL) is automatically achieved and maintained over time by varying the infusion rate according to a three-compartment pharmacokinetic model, with very good predictive performance. The infusion rate is directly and automatically adapted by the software managing the pump, without the need for any of the complex calculations required for a manual scheme.

The ASA guidelines recommend accurate titration of sedative/analgesic medications to improve patients' comfort and safety and avoid the risk of over-sedation<sup>[2]</sup>. Among different systems available for administration of

propofol, the TCI pump is undoubtedly one of the most sophisticated and several studies have shown that target-controlled drug infusion ensures excellent and safe sedation during endoscopic procedures<sup>[30-32]</sup>.

For PCS or PCA, the patient self-administers the medication in response to pain; therefore, the patient must be conscious enough to press the hand-held button. A lock-out time is programmed in order to prevent the delivery of additional doses until the previous dose has taken full effect. PCA, which allows the patient to self-administer frequent, small doses of opioids, as needed to manage pain, could be an effective method for pain control during gastrointestinal endoscopy<sup>[33-35]</sup>.

Pambianco *et al.*<sup>[36]</sup> reported on the investigational computer-assisted personalized sedation system with propofol (CAPS), designed to enable physician-nurse teams to keep patients undergoing endoscopic procedures at minimal to moderate sedation levels, preventing them slipping into deep sedation with drops in cardio-respiratory function. The report described two open-label single-center trials of the CAPS device on 48 patients undergoing either colonoscopy or EGD procedures and found that the results were reproducible across two countries and two practice settings. The system continuously monitors six parameters including oxygen saturation, respiratory rate, heart rate, non-invasive blood pressure, end-tidal carbon dioxide and patients' responsiveness to verbal and tactile stimuli. In this trial the moment-to-moment control of propofol infusion led to very rapid post-procedure recovery from sedation (< 30 s), and the system, also known as SEDASYSTM, performed as designed, reducing or stopping propofol infusion at the first signs of over-sedation, with a very low incidence of desaturation. Pambianco *et al.*<sup>[36]</sup> said that the CAPS device detected apnea more sensitively than clinical observation. In their trial there was no need for airways management or mechanical ventilation.

The CAPS device facilitates the titration of propofol to the desired clinical effect by automatically calculating and delivering a loading dose. The platform continuously checks for early signs of potential adverse effects and the level of sedation, so the physician/nurse teams can adjust the infusion as required, to the targeted degree of sedation. The system is also designed to respond to early signs of over-sedation, as indicated by apnea or hypoxemia, by stopping or reducing delivery of propofol, increasing oxygen delivery and automatically instructing patients to take a deep breath.

In two feasibility studies of CAPS involving 96 patients undergoing elective upper endoscopy and colonoscopy, patients remained minimally to moderately sedated throughout the procedure. For the majority, recovery time was less than 1 min and there were no serious adverse events.

The nurses assisting in the procedures reported that the system was intuitive and user-friendly, and the built-in dosing limits and automated response algorithms allowed the team to be confident that an appropriate level of sedation was being maintained.

A multi-center prospective, randomized, controlled

pivotal trial, presented at Digestive Disease Week in May 2008, compared the safety and effectiveness of propofol plus a single dose of fentanyl administered with the CAPS system, or physician-administered standard sedation regimens involving opioids and benzodiazepines (midazolam with either fentanyl or meperidine) in 1000 patients. Patients who received CAPS sedation had significantly lower measures of cumulative oxygen desaturation than those assigned standard sedation). There were 34 adverse events, no serious adverse events and no rescue interventions among patients sedated with CAPS; there was one rescue intervention in the control group<sup>[37]</sup>. As stated by Pambianco *et al.*<sup>[37]</sup>, the trial investigators, the system made it possible to maintain minimal to moderate sedation with propofol during upper endoscopy and colonoscopy, and helped prevent patients entering deep sedation, which is traditionally associated with propofol.

The system seems to offer a way to personalize the level of sedation appropriate for each patient because it combines propofol delivery with sophisticated monitoring for better control of the sedation regimen, by predicting the patient's level of sedation. Based on the findings of these investigations, the system has been submitted to the US FDA for pre-marketing approval under the brand name SEDASYSTM System.

Most states require the presence of an anesthesiologist during propofol administration, an expensive and unfavorable arrangement for most gastrointestinal endoscopy centers. Current propofol black-box labeling states that only persons trained in general anesthesia should administer the drug. However, pending a favorable FDA review, labeling for the CAPS system will allow physicians and nurses to administer propofol sedation for endoscopic procedures, without the assistance of an anesthesiologist.

In the light of the increasing use of propofol by non-anesthesiologists, some anesthesiologists remain sceptical about CAPS systems, asserting that they cannot substitute for a trained professional, particularly in an emergency. In view of the specific risks of propofol, even if only moderate sedation is intended, patients receiving the drug should receive care consistent with that required for deep sedation, considering the potential for abrupt onset of airway obstruction and apnea and the lack of a specific antidote.

As stated by Iravani<sup>[38]</sup> in a recent editorial, "the intriguing question is whether the use of CAPS in administering propofol prevents the progression of sedation to unintended depths, deep sedation or general anesthesia. In other words, does this precise moment-to-moment control of the propofol infusion titrated to clinical effect obviate the need for the presence of personnel proficient in airway management and advanced life support?"

Could this technology facilitate access to propofol sedation by gastroenterologists? The Anesthesia and Respiratory Device Review panel met on May 28, 2009 and, by an 8-2 margin, approved the CAPS platform for use by endoscopist/nurse teams in EGDS/colonoscopy in ASA I / II adults under the age of 70 years, with BMI < 35 kg/m<sup>2</sup>.

Major hurdles that still remain for propofol adoption are the diversity of medical society guidelines, the costs of anesthesiologist-attended endoscopic procedures, and the immutable, indelible black-box warning about propofol administration. Furthermore, until there is a training program for the use of propofol by non-anesthesiologists, FDA approval of CAPS will probably not be forthcoming.

## DRUGS: WHAT'S NEW?

A number of prodrug formulations of propofol have been developed to overcome the disadvantages of the current lipid-based formulations, including stability, the potential complications of lipid infusion, the risk of contamination and fluctuations in propofol plasma levels due to the bolus injection.

Fospropofol disodium (FD), which now goes by the brand names of Lusedra or Aquavan, is a water-soluble prodrug of propofol with pharmacokinetic and pharmacodynamic properties that differ from propofol emulsion. FD is the first propofol prodrug to be studied for moderate sedation. After IV injection, propofol is released from FD by tissue alkaline phosphatases with a predictable pattern of plasma concentrations, resulting in lower peak concentrations and a more gradual decline in drug concentrations than with a standard propofol injection. Due to the different and complex pharmacokinetics of FD, time to peak sedative effect after a bolus injection is between 3 and 7.5 min, compared with 1 min 36 s for propofol<sup>[39]</sup>.

Although the anesthesiologist community has shown only limited interest, FD has been investigated for sedation by non-anesthesiologists. In 2008 Cohen stated in a review that "FD may be an attractive agent for gastroenterologists interested in realizing the benefits of propofol without the requirement of an anesthesia specialist in the endoscopy suite"<sup>[40]</sup>. In July 2008 the FDA approved FD with a "MAC label", which means that this drug, like propofol, will be used mostly by anesthesiologists and certified registered anesthetist nurses. The drug manufacturer has been in discussions with FDA regarding additional studies and remains committed to getting the product approved for use by non-anesthesiologists.

The ideal drug for sedation for non-anesthesiologists should have certain properties to ensure safe, effective sedation. These include a predictable pharmacokinetic profile, rapid onset of action, analgesic and anxiolytic effects, short recovery time, minimal associated risks and no requirement for the presence of an anesthesiologist. Ketamine<sup>[41,42]</sup>, nitrous oxide<sup>[43,44]</sup> and dexmedetomidine<sup>[45,46]</sup> have all been studied for procedural sedation. While some results have been promising, none fulfil all these criteria or offer any true advance in sedation during gastrointestinal endoscopy.

Remifentanyl, an ultra-short-acting  $\mu$ -opioid receptor agonist, has some advantages over other opioids because of its rapid onset and offset times, making it suitable for controlling pain during endoscopic procedures<sup>[35,47,48]</sup>. The combination of rapid onset and offset of action translates clinically to easy titrability. However, its respiratory depressive

effect has been amply reported<sup>[49,50]</sup>. On account of this, remifentanyl is typically administered in a moderate sedation/analgesia setting, by continuous infusion using a programmable infusion pump. There are many reports of the use of remifentanyl in different settings (obstetrics, gastrointestinal endoscopy, pain control after abdominal surgery) using PCA, with or without background infusion, and the quality of analgesia and patient satisfaction seem to be the same as with standard sedation/analgesia<sup>[35,52-55]</sup>.

New sedatives and delivery systems under development have the potential to improve the quality of endoscopic sedation/analgesia. Scientific societies now need to establish training schemes for the use of sedatives and delivery systems. These should include training in advanced cardiac life support, the pharmacokinetics and pharmacodynamics of the drugs to be used, airway assessment, and training in simple measures of ventilatory support in patients with apnea or airway impairment during sedation for gastrointestinal endoscopy<sup>[15]</sup>.

## CONCLUSION

Most guidelines all over the world recommend the sedation of patients when undergoing gastrointestinal endoscopy. Benzodiazepines combined with opioids are the most frequently used sedative agents; however there are a number of potential concerns/problems with available sedative agents. In fact, most complications in gastrointestinal endoscopy are not related to the procedure, but to sedation and include cardiopulmonary events such as hypoxemia, hypoventilation, airway obstruction, apnea, arrhythmias, hypotension and vasovagal episodes. Finding an ideal regimen of sedation seems to be similar to "Searching the Holy Grail". Since the introduction of propofol in the 1980s, for the induction and maintenance of anesthesia, its clinical application have expanded to include monitored anesthesia care and procedural sedation. The use of propofol for endoscopic sedation has increased markedly during the past 10 years. Several studies have established that propofol is superior to traditional sedative regimens because of its superior recovery profile and its safety profile.

The worldwide safety experience of endoscopist-administered propofol sedation now exceeds 460 000 patients. We look forward to a time when a sedation team will be qualified to administer propofol during gastrointestinal endoscopy without the presence of the anesthesiologist, following a proper training program. The new emerging technology could facilitate access to propofol sedation.

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