The debate for nonanesthesiologist-administered propofol sedation in endoscopy rages on: who will be the “King of Prop?”

Few can argue that propofol is superior to conventional sedative regimens (combination of a benzodiazepine with an opiate) for sedation in endoscopy. The dispute is not whether to use propofol, but who can administer it. Propofol (2,6-diisopropofol) is a sedative that combines the unique properties of rapid onset of action (30-45 seconds) and short duration of effect (4-8 minutes), making it an ideal agent for relatively short outpatient procedures such as upper endoscopy and colonoscopy.1 For these procedures, there are ample data confirming the superiority of propofol to traditional combination regimens in terms of reducing induction and recovery times as well as improved patient satisfaction; these outcomes are achieved without a significant increase in the frequency of serious sedation-related adverse events.2,3 The role of propofol in endoscopic practice is reflected in epidemiologic data predicting an increase in anesthesia-administered sedation from nearly 25% of standard endoscopies in 2007 to more than 50% in 2015.4 If propofol did not offer a more efficient means of sedation, would we be observing this striking shift in anesthesia use? The “propofol phenomenon” epitomizes the challenge of controlling costs while improving quality in the U.S. health care system, where annual costs exceeded $2.3 trillion in 2008 or $7681 per person.5 By increasing the use of anesthesiologist-administered sedation in endoscopy, there is a plausible threat to endoscopist reimbursement by insurance providers in an effort to offset the additional cost.6 Simply stated, the benefits of propofol for sedation in standard endoscopy do not justify the added cost of incorporating an anesthesiologist for low-risk patients.

Although propofol is more efficient than conventional regimens in terms of induction and recovery times, it is only cost-effective compared with standard sedation when administered by a registered nurse under the supervision of the endoscopist.7 Herein lies the fervent debate among gastroenterologists and anesthesiologists.8,9 Anesthesiologists argue that propofol has no reversal agent and is highly potent; therefore, patients sedated with propofol can rapidly transition from a level of moderate sedation to deep sedation or even general anesthesia. This, in turn, could expose the patient to a high risk of sustained hypoxemia and consequent hypoxia-related sequelae such as brain injury and even death. Events surrounding the death of the “King of Pop,” Michael Jackson, in June 2009 created a forum to increase public awareness of the potential hazards of propofol, especially when administered in combination with benzodiazepines and by a nonanesthesiologist.10 Shortly thereafter, the largest experience with nonanesthesiologist-administered propofol (NAAP) was published, summarizing robust safety data that included 223,656 published and 422,424 unpublished cases.11 The momentum for NAAP peaked with a joint statement by the 4 largest GI societies in the United States advocating the use of NAAP for standard endoscopy in low-risk patient populations.12 However, this was promptly countered by the Centers for Medicaid and Medicare Services (CMS), which released a clarification letter to their policy on hospital anesthesia services within days of the societies’ declaration. This effectively shut down long-standing NAAP programs across the United States and closed the door on NAAP, at least for the near term.13

In this issue of Gastrointestinal Endoscopy, Pambianco et al14 offer a unique alternative to standard NAAP by incorporating a computer-assisted, personalized sedation system (SEDASYS; Ethicon Endo-Surgery, Cincinnati, Ohio) into the sedation algorithm. SEDASYS combines comprehensive monitoring (pulse oximetry, capnography, electrocardiography, and noninvasive blood pressure) with an integrated propofol delivery system and an Automated Responsiveness Monitor that measures patient response to auditory and tactile stimuli at regular intervals. Perhaps the most novel aspect of SEDASYS is its ability to adjust the rate of propofol delivery based on data from its monitoring suite and patient feedback via the Automated Responsiveness Monitor; in addition, the endoscopist/
nurse team could administer supplemental bolus doses of propofol. In this industry-sponsored clinical trial, patients undergoing EGD or colonoscopy with American Society of Anesthesiologists class I-III without criteria that would portend a higher risk of sedation-related complications were randomized to a standard combination regimen of benzodiazepine + opiate or propofol-based combination sedation guided by SEDASYS. Although both groups were monitored by using SEDASYS for data collection, the endoscopist/nurse team was blinded to the SEDASYS data in the conventional sedation group (only standard monitoring equipment was used). The authors chose a unique primary outcome measure, area under the curve of oxygen desaturation (AUC\textsubscript{DESAT}), in an effort to quantify not only the depth of hypoxemia but its duration. After consultation with the U.S. Food and Drug Administration (FDA), a sample size of 1000 patients was deemed sufficient to analyze safety and efficacy measures. Patients and physicians were not blinded to the sedation regimen. The study was conducted at 8 sites across the United States, but the number of endoscopists as well as their training and experience with propofol administration and airway management are not provided. This is an important limitation: if all endoscopists in this trial had extensive experience with NAAP, then the incremental benefit of SEDASYS is likely to be minimal and limits the generalizability to practices across the country because the endoscopist/nurse team is already highly skilled in propofol-based sedation.

The study met its primary outcome, with SEDASYS patients having a significantly lower mean AUC\textsubscript{DESAT} (31.3 seconds·%) compared with 81.7 seconds·% in the conventional sedation group. There are 2 potential confounding issues that could have contributed to this observation. First, one of the features of SEDASYS is to automatically increase the oxygen flow rate from 2 L/min to 8 L/min when the pulse oximetry drops to 92% or lower. This may have had an impact on the AUC\textsubscript{DESAT} by preventing desaturation episodes based on the assumption that there is a greater delay in manually providing or increasing supplemental oxygen when the nurse/endoscopist team notes the borderline pulse oximetry reading. Unfortunately, the authors do not disclose how often SEDASYS automatically adjusted the oxygen flow rate; if the device recognizes and reacts to incipient hypoxemia more quickly than the sedation team, this would highlight a benefit of SEDASYS monitoring versus standard monitoring protocols and strengthen the authors’ conclusions. A second factor is the impact of capnography on adverse events. The use of capnography was not standard in the conventional sedation group but available for all patients undergoing sedation via SEDASYS; capnography reduces the incidence of sedation-related complications.\textsuperscript{15,16} This may have resulted in the lower rate of AUC\textsubscript{DESAT} in the SEDASYS group by alerting the sedation team of impending apnea, thereby leading to noninvasive airway maneuvers, adjustment of sedation, or increase in oxygen supplementation. Patient and clinician satisfaction scores were significantly higher in the SEDASYS group, although the clinical relevance of these observed differences is probably minimal. As expected, SEDASYS patients recovered more quickly (99% within 10 minutes compared with 75% in the conventional group). These results are in line with those of previous studies of propofol in endoscopy; there are dramatic differences in patient recovery (ie, the superior efficiency of propofol sedation is marked) coupled with modest improvements in patient and clinician satisfaction. However, the absence of physician and patient blinding in this trial reduces the validity of the observed differences in satisfaction scores. Although there were no serious sedation-related complications in the study, 5.8% of SEDASYS and 8.7% of conventional sedation patients experienced an adverse event; the authors do not specify whether this was a statistically significant difference, and details are not provided in their article.

Depth of sedation is an important aspect of this trial because a principal issue with propofol administration by nonanesthesiologists is its propensity to induce unintentional deep sedation/general anesthesia and consequent sedation-related cardiopulmonary complications. Only 0.5% of Modified Observer’s Assessment of Alertness/Sedation scores decreased to 0 or 1 (consistent with deep sedation/general anesthesia); stated alternatively, 12 of the SEDASYS patients (2.4%) and 5 of conventional sedation patients (1.0%) met the criteria for deep sedation or general anesthesia. From the optimist’s perspective (eg, the endoscopist), this is not a statistically significant difference. From a regulatory perspective (FDA, CMS, anesthesiology providers), more patients inadvertently progressed to deep sedation or general anesthesia with propofol, highlighting the potency of this sedative. Despite this fact, the duration of apnea was significantly longer and the rate of cardiorespiratory events was significantly higher in the conventional sedation subgroup. Even though the level of sedation was minimal to “light moderate” (defined as an Modified Observer’s Assessment of Alertness/Sedation score of 4) in most subjects, patient satisfaction scores across the entire study population were high and suggest a particularly motivated patient population; a higher percentage of patients undergoing standard endoscopic procedures using conventional sedation regimens unintentionally reach a level consistent with deep sedation.\textsuperscript{17,18} Additionally, patients in this study population were also uncharacteristically thin, with few patients in either group having a body mass index greater than 30 kg/m\textsuperscript{2}, limiting the generalizability given that the prevalence of obesity in the United States is at least 27%.

Do the findings from this study reassure the FDA, American Association of Nurse Anesthetists, American Society of Anesthesiologists, and CMS that computer-assisted NAAP (CatNAAP) is a viable alternative to conventional sedation for low-risk patients undergoing
low-risk endoscopy? The authors have nicely demonstrated that CATNAAP is at least equivalent if not superior to conventional sedation in terms of safety and definitely superior in terms of recovery time. However, how much of the data can be attributed to skilled nurse/endoscopist teams and select patient population and how much are attributed to the “intuition” of the automated monitoring system? The authors do not detail the frequency with which SEDASYS “reacted” to data during the procedure: how often did the device increase or decrease the dose of propofol based on physiologic parameters and Automated Responsiveness Monitor data? How often did the endoscopist have to override SEDASYS and administer a bolus of propofol? In their executive summary to Ethicon Endo-Surgery, the FDA notes 77% of procedures required at least 1 bolus administration by the endoscopist, and 27% of all propofol administered in the trial was via an endoscopist-directed propofol bolus.19

Did SEDASYS prevent hypoxemia by increasing oxygen supplementation based on physiologic data? More than half of patients who developed “incipient hypoxemia,” defined as a pulse oximetry less than 92%, progressed to SaO2 less than 90%; would this have been higher in a NAAP protocol without SEDASYS? Does SEDASYS make NAAP safer? To determine the incremental benefit of SEDASYS in preventing sedation-related complications would require a randomized clinical trial comparing NAAP with and without the assistance of SEDASYS monitoring and drug administration.

Pambianco et al have contributed to the large body of literature that demonstrates the safety and efficacy of NAAP. Their study evaluates a unique derivative of NAAP, as they have added computer assistance to a NAAP protocol (CATNAAP). In this well-designed randomized clinical trial of CATNAAP, the authors demonstrate that the safety profile is comparable to that of conventional sedation regimens in low-risk patients undergoing standard endoscopic procedures. However, because the study was sponsored by the manufacturer of SEDASYS, we should be particularly critical of the results. Where do we go from here? Cost and manpower issues dictate that anesthesia-administered sedation in endoscopy cannot expand uncontrollably in the years to come. The use of CATNAAP may offer added security in trying to minimize sedation-related complications. However, we would be remiss in assuming that purchasing SEDASYS for our endoscopy units will remove the need to undergo rigorous training in propofol administration and noninvasive airway rescue maneuvers such as placement of an oral airway and positive pressure ventilation. Should such systems become FDA approved, it is still important for gastroenterologists and registered nurses using such systems to complete a training program in propofol administration along with airway management before initiating CATNAAP at their facility. Such a training program needs to be explicitly developed and overseen by anesthesiologists. For SEDASYS or an alternative device that assists in the administration of propofol to gain approval, the FDA will need to address current regulations restricting the use of propofol to anesthesia providers. It must also be emphasized that appropriate patient selection for NAAP is pivotal, and CATNAAP may further improve safety by incorporating a meticulous physiologic monitoring/drug administration device into the sedation algorithm. To use a common euphemism heard by political pundits in recent years, gastroenterologists and anesthesiologists must collaborate on a bipartisan solution to “the propofol problem.”

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Gregory A. Coté, MD, MS
Indiana University School of Medicine
Indianapolis, Indiana, USA

Abbreviations: AUCDESAT, area under the curve of oxygen; CATNAAP, computer-assisted nonanesthesiologist-administered propofol Desaturation; CMS, Centers for Medicaid and Medicare Services; FDA, U.S. Food and Drug Administration; NAAP, nonanesthesiologist-administered propofol.

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