

## Computer-assisted personalized sedation

*The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of new or emerging endoscopic technologies that have the potential to have an impact on the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent preclinical and clinical studies on the topic, and a MAUDE (Manufacturer and User Facility Device Experience; U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the “related articles” feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized but, in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. For this review, the MEDLINE database was searched through January 2010 using the keywords “computer,” “computerized,” “computer-assisted,” “sedation,” “propofol.”*

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The vast majority of endoscopic procedures are performed with patients under sedation, typically with intravenous administration of a combination of an anxiolytic agent (eg, midazolam) and an opioid analgesic agent (eg, fentanyl). The efficiency and throughput of endoscopy units can be improved considerably by reducing the time to achieve sedation and shortening postprocedure recovery.<sup>1</sup> In addition, improved patient sedation may increase

patient satisfaction and compliance with screening and surveillance procedures.

Propofol (2,6-diisopropylphenol) offers the advantages of a rapid onset of action, the ability to achieve adequate sedation, and a short half-life, leading to rapid recovery. It is estimated that propofol is currently used in approximately 25% to 33% of endoscopic procedures performed in the United States and, given its advantages, there is the potential for significant growth in its use.<sup>2,3</sup> Factors limiting this growth include inadequate numbers of trained anesthesiologists and the increased cost associated with an anesthesiologist providing sedation for routine endoscopic procedures. Administration of propofol sedation by an endoscopist-nurse team is, therefore, an attractive proposition, and several studies have evaluated the safety of physician- and nurse-administered propofol sedation.<sup>4,5</sup> However, the American Society of Anesthesiologists (ASA) and the drug labeling both recommend administration of propofol only by persons trained in the administration of general anesthesia.<sup>6-8</sup> The rationale for this stance is propofol's narrow therapeutic window with the potential for rapid unintended progression from moderate sedation to deep sedation or general anesthesia. The lack of a reversal agent is also raised as a concern, but propofol has a very short half-life, which is associated with rapid recovery.

Administration of propofol sedation by the endoscopist-nurse team may arguably be imprecise because judging the depth of sedation, comfort, and safety consistently throughout the procedure may be compromised by distractions inherent in endoscopic procedures. Even when administered during a colonoscopy by an anesthesiologist, the therapeutic index is low and excess sedation may occur.<sup>9</sup> Computer-assisted personalized sedation (CAPS) devices seek to make the delivery of propofol sedation predictable, precise, and safe by using computer algorithms to calculate and deliver appropriate amounts of propofol, based on quantifiable physiological parameters.

### EMERGING TECHNOLOGY

The SEDASYS CAPS system (Ethicon Endo-Surgery Inc, Cincinnati, Ohio), is designed to facilitate the safe administration of 1% propofol-based minimal to moderate sedation to relatively healthy adults (ASA physical status I and II) undergoing elective colonoscopy or EGD, by an endoscopist-nurse team whose members are not trained in

general anesthesia. It is not intended for administration of deep sedation or general anesthesia or administration of any level of sedation to high-risk patients. The system was designed to comply with the practice guidelines for sedation and analgesia by nonanesthesiologists developed by the ASA,<sup>10</sup> as well as the dosing guidelines in the U.S. Food and Drug Administration (FDA)–approved propofol labeling. The Anesthesiology and Respiratory Therapy Devices Advisory Panel of the FDA voted in favor of approval of the SEDASYS system in May 2009. However, in April 2010, the manufacturer received a not-approvable letter from the FDA. The manufacturer appealed this decision and the FDA has granted the appeal.<sup>11</sup> A new independent advisory panel will be appointed to reconsider the clinical trial data. The device has been approved in Canada for sedation of patients undergoing colonoscopy, in Australia for sedation of patients undergoing colonoscopy and EGD, and in May 2010 was granted the Conformité Européenne (CE) mark of approval in the European Union for use during routine colonoscopy and EGD.<sup>12,13</sup>

Physiological patient data (oxygen saturation, capnometry, respiratory rate, heart rate, blood pressure, electrocardiography, and patient responsiveness) are monitored continuously by the device. The device then processes these physiological data and, using a computerized drug delivery algorithm, is able to titrate sedation by varying the propofol infusion and administering boluses of propofol. It is also able to increase oxygen delivery in response to hypoxemia and apnea.

The 2 major subsystems of the device are the bedside monitoring unit (BMU) and the procedure room unit (PRU). The BMU is a mobile unit that is attached to and moves with the patient through the pre-, intra-, and post-procedure periods. This unit has a port for attachment of an oronasal cannula for oxygen delivery and monitors and displays the oxygen saturation, noninvasive blood pressure, and electrocardiographic data. The BMU also incorporates the automated responsiveness monitor (ARM) designed to assess patient responsiveness. At preset intervals, it delivers to the patient an auditory request (“please squeeze the handset”) together with a mild vibration of the handset. If the patient fails to respond by squeezing the handheld switch, the verbal request becomes louder and more commanding (“squeeze the handset now”) and the handset vibration more vigorous. The ARM calculates and displays the patient response time to these stimuli and deems a lack of patient response within 14 seconds as unresponsive. Previous studies have demonstrated that the loss of ARM response precedes development of deep sedation and adverse physiological effects.<sup>14</sup>

The PRU integrates patient monitoring to propofol and oxygen delivery. It incorporates a capnometry device, an oxygen regulator, a peristaltic infusion pump, and the software program/algorithms that drive the pump. These algorithms are based on pharmacokinetic principles, determining the loading dose based on the product of the

target serum propofol concentration and the volume of distribution. Similar principles are used to subsequently calculate increases or decreases in target serum propofol concentrations.

On patient entry into the procedure room, the BMU is connected by a cable to the PRU. Physiological parameters previously displayed on the BMU are now transferred to the PRU monitor, which displays the respiratory rate, end tidal CO<sub>2</sub> and capnogram, arterial oxygen saturation, heart rate, noninvasive blood pressure, electrocardiography, and the patient response time. There is also an interface that allows control of the rate of propofol infusion and of bolus administration. The PRU has a backup battery to allow continued safe infusion in the event of a power outage.

The health care provider is able to select an initial propofol maintenance rate, with a maximum of 75 µg/kg/min. The software algorithm then calculates and delivers an initiation loading dose over 3 minutes at a constant infusion rate, after which it delivers propofol at the set maintenance rate. The health care provider is able to subsequently increase (or decrease) the infusion rate, based on the patient’s sedation state. There is a 3-minute lockout after initiation or after any subsequent maintenance rate increase. A bolus feature also allows the provider to manage transient episodes of patient discomfort with a propofol dose of 0.25 mg/kg delivered over 10 to 30 seconds. There is a 90-second lockout after a bolus dose. On decreasing the infusion rate, the algorithm stops the infusion for a calculated period to allow drug elimination before reinitiating infusion at the lower rate. The health care provider may also stop the infusion when the procedure is near completion.

The device is equipped with several safety mechanisms. It does not allow propofol infusion unless oxygen is being delivered to the patient. Indicators of oversedation such as oxygen desaturation, a low respiratory rate, and apnea, trigger the system to respond by increasing oxygen delivery rate from its baseline of 2 L/min sequentially up to 12 L/min. The device assesses patient responses to the verbal and tactile stimuli and incorporates restrictions based on these responses. The system automatically decreases the maintenance rate when responsiveness to the ARM is lost. As a further safeguard, the system also ties the maintenance rate increase limits to the patient response time as determined by the ARM.

The system has visual and audible alarms at 2 levels (yellow and red) to alert the endoscopist to negative physiological parameters including hypoxia, apnea, tachycardia/bradycardia, and hypotension/hypertension. Activation of these alarms by hypoxia or apnea leads to temporary interruption of propofol infusion. After a yellow alarm, the propofol is then reinitiated at a lower maintenance rate. After the higher level red alarm, triggered by hypoxia with prolonged apnea, the infusion can only be reinitiated by the physician or nurse when he or she believes this to be appropriate. The device also repeatedly commands the patient to take a deep

breath. Finally, the system also displays advisories that alert the clinician to both correctable hardware problems and uncorrectable failure of any of the subsystems.

## CLINICAL RESULTS

Closed-loop systems to monitor and deliver sedation to patients have long been an attractive proposition, and a computerized algorithm to assist with propofol sedation during endoscopy was initially described in 1991.<sup>15</sup> The authors evaluated a computer-controlled pump-delivery system that used a mathematical model for the pharmacokinetic behavior of propofol to calculate an infusion rate designed to achieve and maintain a predicted target blood concentration for propofol. The first feasibility assessment of CAPS with the SEDASYS system was published in abstract form in 2006.<sup>16</sup> The study assessed the driving software of the system when used by an anesthesiologist in the sedation of 24 subjects undergoing colonoscopy or EGD. After a single dose of fentanyl as premedication, propofol was administered using the device. Oxygen desaturation to less than 90% developed in only 1 study subject; apnea persisting for 30 seconds or longer developed in 7 subjects. Automated device actions in response to these events resulted in spontaneous successful recovery of all patients to normal respiratory parameters. Patient satisfaction scores related to sedation were high.

A subsequent article detailed 2 open-label, single-center studies assessing the performance of CAPS with the SEDASYS system when used by endoscopist-nurse teams to administer propofol sedation.<sup>17</sup> Twenty-four ASA class I, II, or III subjects undergoing EGD or colonoscopy were recruited at each center. After an initial dose of fentanyl, propofol was administered at an initial rate of 75  $\mu\text{g}/\text{kg}/\text{min}$  and then titrated to achieve the desired sedation effect. Propofol delivery was stopped or decreased during endoscope withdrawal. Recovery times (colonoscopy/endoscope removal to an Aldrete score of  $\geq 12$ ) were shorter than 30 seconds for all procedures. High levels of satisfaction with CAPS were noted by both endoscopists and patients. The device performed safely with oxygen desaturation (defined as  $\text{SpO}_2 < 90\%$  for  $> 15$  seconds) noted in only 3 study subjects (6%) for durations ranging from 16 to 45 seconds. Eighteen subjects (38%) experienced at least 1 episode of apnea lasting 30 seconds or longer. No subjects required airway support, and no hypotension or bradycardia developed in any subject. Importantly, the device achieved moderate sedation using one third of the total propofol dose reported in a previous nurse-administered propofol sedation (NAPS) trial.<sup>5</sup> More than 21,000 individual decisions were reportedly made by the SEDASYS device in the course of this study, and a postprocedure assessment by anesthesiologists agreed with all clinically significant decisions.

Recently, a large, randomized, unblinded, multicenter study compared SEDASYS with standard sedation (opioids

plus benzodiazepines) in ASA class I, II, and III subjects undergoing colonoscopy ( $n = 721$ ) or EGD ( $n = 279$ ).<sup>18</sup> The primary endpoint, a decrease in the area under the curve of oxygen desaturation, which represents the degree and duration of hypoxia, was not achieved by the SEDASYS system for EGD, but was reportedly achieved for colonoscopy. However, a marked study-site effect was noted.<sup>19</sup> The FDA analysis indicated that investigator behavior (hypoxia failing to consistently trigger an increase in oxygen delivery at 2 study sites in the standard sedation arm) rather than product performance may have biased results in favor of the SEDASYS system. Several secondary endpoints were achieved. Clinicians were more satisfied with sedation provided by the SEDASYS system than with standard sedation. Recovery from sedation was significantly faster with the SEDASYS system in both procedure groups. Two colonoscopy patients (1%) were unable to complete the study because of device failure. Of patients in the SEDASYS arm undergoing colonoscopy, 10 (3%) experienced deep sedation or general anesthesia; the longest period was 16 minutes compared with 4 patients (1%) in the conscious sedation group (longest period 22 minutes). In the SEDASYS group, hypoxemia, as defined in the previous study,<sup>11</sup> was noted in 6% of patients compared with 22% of the conscious sedation group. Additional events in the SEDASYS group included hypotension in 2% and bradycardia in 3% of colonoscopy patients, which was similar to the conscious sedation group. No deaths or hospitalizations occurred. Airway intervention was necessary in only 1 patient in both groups.

## POTENTIAL APPLICATIONS

The intended use of CAPS devices is to facilitate the administration of propofol-based minimal to moderate sedation to adults undergoing colonoscopy or EGD by an endoscopist-nurse team not trained in general anesthesia. It is likely that CAPS devices will subsequently be evaluated for other procedures performed with the patients under sedation.

## RESEARCH AGENDA

At this time, the FDA regulatory assessment and the recent Centers for Medicare and Medicaid Services guideline indicating that propofol administration for deep sedation should only be performed by anesthesiologists remain major obstacles to the incorporation of this technology into endoscopic practice in the United States.<sup>20</sup> Although the results of initial studies are encouraging, they are limited by the open-label design. Further large, randomized, controlled, multicenter studies evaluating the safety and efficacy of CAPS in patients undergoing endoscopy should be performed. If eventually approved by the FDA, postmarketing safety studies should be undertaken. The safety of CAPS in older patients, ASA class III and IV

patients, and patients undergoing prolonged endoscopic procedures such as ERCP and EUS should be evaluated, perhaps initially by anesthesiologists. Studies should also establish the appropriate training necessary for physicians and nurses and the number of health care personnel needed in procedure rooms to safely use CAPS.

Studies should also be performed comparing CAPS, nurse-administered propofol sedation, balanced propofol sedation (combination of low-dose opioid and propofol), and monitored anesthesia care (MAC). In addition, CAPS devices should be compared with other approaches to propofol sedation, including patient-controlled drug delivery systems and serum concentration target-controlled infusion.<sup>21-23</sup> Future study outcomes should include parameters evaluating safety, efficacy, and patient/endoscopist satisfaction. Finally, studies evaluating the cost benefit of CAPS and its impact on practice efficiency relative to standard sedation and MAC are needed.

## SUMMARY

CAPS systems offer the possibility of safe and effective minimal to moderate propofol sedation by health care professionals who are not trained in general anesthesia. Preliminary studies with the SEDASYS system suggest that the device is safe for use in ASA class I and II subjects undergoing routine endoscopy. Further studies are needed to define its role in high-risk patients and in advanced procedures. Regulatory issues remain a major obstacle to adoption of the device in the United States.

*Abbreviations:* ARM, automated responsiveness monitor; ASA, American Society of Anesthesiologists; ASGE, American Society for Gastrointestinal Endoscopy; BMU, bedside monitoring unit; CAPS, computer-assisted personalized sedation; FDA, U.S. Food and Drug Administration; PRU, procedure room unit.

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