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What's new in sedation techniques for ambulatory procedures

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INTRODUCTION

Sedation techniques have become increasingly popular for a wide variety of both diagnostic and therapeutic procedures performed on an ambulatory basis. The commonly used sedative-hypnotics produce a dose-dependent spectrum of central nervous system (CNS) depression which represents a continuum from minimal («light») to deep sedation. The three commonly used terms to describe the various levels of sedation are:

I. **Minimal Sedation («Premedication»)** is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be mildly impaired, ventilatory and cardiovascular functions are unaffected.
II. **Moderate Sedation («Conscious Sedation»)** is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or when accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually unaffected.
III. **Deep Sedation («Intravenous Anesthesia»)** is a drug-induced depression of consciousness during which patients cannot be easily aroused, but may respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Although bradycardia can occur, cardiovascular function is usually maintained.

Recent data from an ASA Closed Claims study[1] involving patients receiving monitored anesthesia care (MAC) demonstrates that medical legal claims typically involved older and sicker patients than claims involving general anesthesia. The percentage of claims which resulted in permanent brain damage or death was equivalent to that seen with general anesthesia! Over 50% of the claims were judged to be preventable by better monitoring, including capnography, increased vigilance, or audible alarms, and all of these claims by definition involved an anesthesiologist. In 41% of these cases, the anesthesia care was judged to be «substandard» and financial payments were made in 51% of these cases, with a median payment of $159,000.

Published reports involving sedation by non-anesthesiologists using a variety of sedative-analgesic medications generally report only «rare» adverse outcomes. However, a recent study by Patel et al[2] found that deep sedation occurred in 68% of patients undergoing GI endoscopy with meperidine and midazolam, with patients undergoing ERCP (83%) and endoscopic ultrasonography (80%) procedures being at the highest risk. Adverse outcomes in a number of series have been associated with co-existing diseases, particularly respiratory impairment[3]. If sedation is to be provided by non-anesthesiologists, careful screening and patient selection is critically important. In the initial experiences where gastroenterologists administered propofol during endoscopic procedures, a second gastroenterologist administered the sedation-analgesia. Subsequent larger series[3] used a special sedation nurse who had received extensive training to administer propofol. In a small comparative study involving gastroenterologist-administered propofol *vs* meperidine/midazolam when using capnography to monitor respiratory rate (and airway patency), Vargo et al[4] reported similar physiological outcomes and pa-

tient/endoscopist satisfaction. They also stated that the use of propofol in this GI population led «to significantly improved recovery of baseline activity and food intake 24 h after the procedure.» However, the ASA has developed specific guidelines for sedation and analgesia by non-anesthesiologists, including the use of propofol.

COMMONLY USED MEDICATIONS

The spectrum of adjuvant drug therapies used during sedation procedures includes sedative-hypnotic drugs with anxiolytic properties to minimize the «stress» associated with the operating room environment, drugs with amnestic properties to reduce recall of events during the procedure, sympatholytic drugs to maintain hemodynamic stability, and analgesic medication to optimize patient comfort (Table I). Ideally, the drug (or combination of drugs) used would be easily titrated to rapidly achieve the desired effects (i.e., a predictable dose-effect relationship), have a low incidence of perioperative side effects, and allow for a rapid spontaneous recovery to baseline activity levels. As the ideal drug is yet to be found, careful titration of the available drug(s) to achieve the desired clinical effects may be more important than the choice of any individual drugs, particularly in elderly patients and those with pre-existing medical diseases. The most commonly used sedative-analgesics are listed in the table below:

A wide of barbiturate compounds have been used for sedation during diagnostic and therapeutic procedures (i.e., «conscious sedation» and MAC, respectively)[6]. Although thiopental may be associated with a prolonged recovery time, methohexital provides excellent intraoperative sedation and a rapid recovery when administered by either intermittent bolus injections (10-20 mg) or as a variable-rate infusion. While studies involving the use of bolus injections suggested that residual sedation was greater with methohexital than propofol[7], Sá Rêgo et al[8] showed no significant differences in the recovery times when infusions of methohexital (40 $\mu g.kg^{-1}.min^{-1}$) and propofol (50 $\mu g.kg^{-1}.min^{-1}$) were compared during MAC cases. As expected, propofol was associated with a higher incidence of pain on injection (23 *vs* 10%).

Among the available benzodiazepines, midazolam is more acceptable than either diazepam or lorazepam. Compared to diazepam, midazolam is associated with less pain on injection and venous irritation. Midazolam also produces more profound amnesia than diazepam, and less residual (post-procedural) amnesia than lorazepam. The time required to achieve a peak CNS effect with midazolam (3-5 min) may lead to cumulative effects («oversedation») when repeated bolus doses are administered at frequent time intervals. White et al[9] noted a similar spectrum of CNS depression with midazolam (0.05 to 0.15 $mg.kg^{-1}$, IV) and diazepam (0.1 to 0.3 $mg.kg^{-1}$, IV). However, midazolam possesses a smaller margin of safety with

Table I. Recommended dosages of commonly used sedative-hypnotic and analgesic drugs†.

Drug group	Bolus dosages	Infusion rates
Sedative-hypnotics		
• Diazepam	5-10 mg	
• Midazolam	2.5-7.5 mg (alone)	
	1-2 mg (with propofol)	1-2 $\mu g \bullet kg^{-1} \bullet min^{-1}$
• Propofol	25-100 mg	25-100 $\mu g \bullet kg^{-1} \bullet min^{-1}$
• Thiopental	50-200 mg	
• Methohexital	5-20 mg	15-60 $\mu g \bullet kg^{-1} \bullet min^{-1}$
Sedative-analgesics		
• Ketamine	10-20 mg	5-20 $\mu g \bullet kg^{-1} \bullet min^{-1}$
• Dexmedetomidine	30-60 µg	0.01-0.02 $\mu g \bullet kg^{-1} min^{-1}$
Analgesics		
• Meperidine	25-100 mg	
• Alfentanyl	150-500 µg	0.5-1 $\mu g \bullet kg^{-1} \bullet min^{-1}$
• Fentanyl	25-100 µg	
• Remifentanyl	5-20 µg	0.025-0.1 $\mu g \bullet kg^{-1} \bullet min^{-1}$

† In the elderly population, lower dosages of the sedative-analgesic drugs should be administered (e.g., midazolam 0.5-1.0 µg IV, propofol 10-50 µg/kg/min) to avoid prolonged recovery times.

respect to ventilatory depression, and requires and greater need for careful titration to achieve the desired clinical end-point without untoward side effects. The lipid-based formulation of diazepam is associated with a lower incidence of both pain and venoirritation than the original propylene glycol formulation[10]. When midazolam is administered a continuous infusion (loading dose of 0.025-0.05 $mg.kg^{-1}$ followed by a maintenance infusion of 1-2 $\mu g.kg^{-1}.min^{-1}$), it can provide for a titratable level of sedation. While midazolam provides more effective perioperative amnesia than methohexital or propofol, its use is associated with a slower recovery of psychomotor function[4,11].

Propofol has pharmacokinetic and recovery characteristics which make it ideally suited for use during procedures requiring moderate-to-deep sedation. Low-dose propofol infusions have been used as an adjuvant to local anesthesia in patients undergoing a wide variety of diagnostic (e.g., endoscopic) and superficial surgical procedures in the operating room (e.g., breast biopsy and herniorrhaphy). In comparing propofol and midazolam infusions for sedation during MAC procedures, the use of propofol was associated with a more rapid recovery of cognitive function and less postoperative sedation, drowsiness, confusion, clumsiness, and amnesia than midazolam[11]. Compared to midazolam and methohexital, use of propofol is associated with the lowest incidence of awareness during insertion of an endoscope and at the time of the initial injection of the local anesthetic[4,11]. Furthermore, use of propofol resulted in more satisfactory conditions during the remainder of the procedure. Since subhypnotic doses of propofol are associated with minimal intraoperative amnesia, a small «premedicant» dose of midazolam (0.5-2 mg IV) has been found to be beneficial in enhancing propofol-induced sedation, amnesia and anxiolysis during the procedure without delaying recovery[12]. Although pain on injection remains the most commonly reported side effect with propofol, newer generic and median chain triglyceride (MCT) formulations of propofol appear to be associated with somewhat less discomfort during the initial injection[13]. Unfortunately, a new lower lipid formulation of propofol (Ampofol) was associated with slightly greater pain on injection[14]. A novel water-soluble cyclodextrin propofol formulation was also reported to produce more pain on injection than the standard lipid-containing formulations of propofol[15]. In contrast, the new water-soluble prodrug formulation of propofol (Aquavan) does not appear to produce significant pain on injection[16,17].

Ketamine produces a unique «dissociative» sedative-anesthetic state[18]. However, it can also produce undesirable cardiovascular stimulation and unpleasant psychomimetic emergence reactions. In low doses (50-100 µg/kg) ketamine produces mild sedation and analgesia without untoward CNS effect, and has proven to be useful in treating transient discomfort in patients receiving local anesthesia for diagnostic or minor therapeutic procedures. Since even relatively low-doses of ketamine can be associated with CNS side effects, benzodiazepines are often co-administered to attenuate the psychomimetic effects of ketamine[18]. More recently, the combination of propofol and ketamine has been used to provide sedation and analgesia during minor procedures[19]. By avoiding opioid analgesics, this popular combination can provide for a «deep» level of sedation without excessive ventilatory depression[20].

Remifentanyl is unique among the potent opioid analgesics because of its extremely short elimination half-time (3-5 min) due to rapid esterase metabolism. Remifentanyl has been used as an alternative to both meperidine-midazolam[21] and propofol[22]. However, its use possesses a greater risk of ventilatory depression and postoperative nausea and vomiting. Remifentanyl-induced ventilatory depression is enhanced by concomitant sedative medication (e.g., midazolam) in a dose-related fashion[23]. Finally, dexmedetomidine has been more recently introduced as an alternative to propofol[24]. However, use of dexmedetomidine as a sole agent for colonoscopy was less than ideal, and was associated with more complications than a standard combination of meperidine and midazolam[25].

In the future, several newer sedative-hypnotics and sedative delivery systems are likely to be introduced. Two new compounds which may be available for clinical use in the future are shorter-acting benzodiazepine (Ro 48-6792), and a prodrug which is rapidly converted to propofol (AquavanÔ). A derivative of midazolam, Ro 48-6792, was initially evaluated as an alternative to midazolam for sedation during colonoscopy[26]. Use of Ro 48-6792 was associated with a slightly faster recovery; however, patients required more opioid analgesic during the procedure. Although Aquavan lacks propofol's pain on injection[16,17], questions remain regarding its ease of titration and the incidence of perineal dysesthesias (e.g., burning sensation). Clearly, more clinical testing is needed to determine the future role of Aquavan in procedural (as well as MAC) sedation. Finally, novel systems for delivering «old drugs» are in developmental stages (e.g., a propofol sedation drug delivery system). Indeed, future options for sedation of patients undergoing diagnostic and therapeutic procedures should offer some exciting new possibilities for practitioners.

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