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ENDOSCOPY MINISERIES

Optimal sedation for gastrointestinal endoscopy: Review and recommendations

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Abstract

Sedation practices for endoscopy vary widely. The present review focuses on the commonly used regimens in endoscopic sedation and the associated risks and benefits together with the appropriate safety measures and monitoring practices. In addition, alternatives and additions to intravenous sedation are discussed. Personnel requirements for endoscopic sedation are reviewed; there is evidence presented to indicate that non-anesthetists can administer sedative drugs, including propofol, safely and efficaciously in selected cases. The development of endoscopic sedation as a multi-disciplinary field is highlighted with the formation of the Australian Tripartite Endoscopy Sedation Committee. This comprises representatives of the Australian and New Zealand College of Anaesthetists, the Gastroenterological Society of Australia and the Royal Australasian College of Surgeons. Possible future directions in this area are also briefly summarized.

Introduction

The number of gastrointestinal endoscopic procedures carried out worldwide has increased substantially over the last decade. In Australia, for example, there were over 690 000 endoscopic procedures reimbursed by Medicare for the year commencing 1 July 2007.[1] The vast majority of endoscopies are done with the aid of intravenous sedation, and this practice seems highly likely to continue. There are key elements of endoscopic practice that have implications for sedation (Table 1).

Physician and surgeon endoscopists have a duty of care to their patients to strive to minimize pain and discomfort. However, this objective should be tempered by minimization of adverse events related to the procedure (e.g. perforation or bleeding) and to the sedation (hypoxemia, aspiration, cardiac events).

The present review focuses on the evidence base with respect to intravenous sedation for gastrointestinal endoscopy, endeavoring in the process to formulate guidelines for best practice in this area. Key points and recommendations are summarized in the Appendix. The motivation of the authors is not to be proscriptive but to inform and stimulate further constructive discussion in this important area.

Definition of sedation

According to the American Society of Anesthesiologists (ASA), 'Sedation and analgesia comprise a continuum of states ranging from minimal sedation (anxiolysis) through general anesthesia.'[2] It is important to recognize this continuum as summarized in Table 2. A change in the level of sedation from conscious sedation to general anesthesia may occur inadvertently with a relatively small alteration in the dose of sedative drugs used. This continuum of sedation advocated by the ASA has also been adopted by the Tripartite Committee of the Australian and New Zealand College of Anaesthetists (ANZCA), Gastroenterological Society of Australia (GESA) and Royal Australasian College of Surgeons.[3]

Goals of sedation for endoscopy

The goals of sedation are to achieve a balance between the benefits of sedation (Table 3) versus potentially avoidable risks (Table 4).

Mortality and cardiorespiratory morbidity

Reported risks of endoscopy vary widely. A Scottish study reported a mortality rate of 153 out of a total of 33 854 patients.[4] Over 90% of the deaths were in ASA grade III, IV or V cases (Table 5). In a group of almost 650 000 patients, a recent multinational study[5] reported four post-procedure deaths, only one of which was attributable to factors related to sedation, giving an anesthetic death rate of 0.0002%. It is of note that, in contrast to the Scottish study, very few cases were carried out outside of ambulatory care settings and no endoscopic retrograde cholangio pancreatographies (ERCPs) were included.

In terms of cardiorespiratory morbidity of endoscopy procedures, a survey commissioned by the American Society for Gastrointestinal Endoscopy (ASGE) revealed a rate of

cardiopulmonary complications of 0.54%.[6] Other reported rates have varied from 0.02% to 0.37%.[7] The recent multi-national study[5] of 646 080 patients revealed a very low overall risk of cardiorespiratory complications; 0.1% required bag and mask ventilation for upper endoscopy and 0.01% for colonoscopy. Endotracheal intubation was required in only four patients, and only one patient sustained neurologic injuries. The wide variation in complication rates can be attributed to differences in study design, patient population, methods of sedation and definitions of complications. In addition, some endoscopic procedures, such as ERCP have been shown to be more likely to lead to cardiorespiratory complications, particularly in elderly patients.[8] The exact contribution of the sedation process to post-procedure cardiorespiratory complications can be difficult to determine, particularly in patients with ASA grade IV and above.

Alternatives and additions to intravenous sedation

Unsedated endoscopy

Surveys have indicated that a substantial proportion of patients in Asia, Europe and Canada undergo upper gastrointestinal endoscopy without sedation.[9] This practice is not common in the USA and Australia. There is evidence that the low prevalence of unsedated endoscopy is due more to patient reluctance rather than physician preference.[10] In terms of patient tolerance, a double-blind Finnish study compared intravenous midazolam alone compared with each of three other groups: a placebo-controlled no sedation group, a placebo-controlled pharyngeal local anesthetic group, and a third control group that was unblinded.[11] The patients in the midazolam group were found to be more likely not to remember the procedure and reported more willingness to return for a repeat procedure. The effects were most pronounced in younger patients. In terms of endoscopist assessment, the patients in the midazolam group were rated as easier to intubate by the endoscopist compared with the placebo group, but there was no difference between the midazolam group and either the pharyngeal anesthesia or control groups. Interestingly, the midazolam group

Table 1 Aspects of endoscopic practice with implications for sedation

1	The vast majority of procedures are performed as day cases. The procedure and recovery times are thus short as shorter acting agents are advantageous
2	Due to their short duration and absence of skin incisions, endoscopic procedures are generally not associated with significant fluid shifts or medication-requiring post-procedure discomfort
3	The level of sedation required to prevent discomfort during the procedure varies, and can change both suddenly and unpredictably
4	Many patients are medically very well—an increasing number are presenting for screening procedures
5	To the extent that most patients are not intubated for endoscopic procedures, the airway is not protected. In the case of upper gastrointestinal endoscopy, endoscopic retrograde cholangio pancreatography (ERCP) and endoscopic ultrasound, the presence of the endoscope impairs ready access to the airway and makes positive pressure ventilation difficult

Table 3 What we are trying to achieve in sedation for endoscopy

- Alteration of consciousness, mood and anxiety
- Amnesia
- Analgesia
- Patient cooperation
- Maintenance of intact airway and airway reflexes
- Hemodynamic stability
- Early safe post procedure discharge

Table 4 What we are trying to avoid in sedation for endoscopy

- Patient aggravation
- Deep unrousable state
- Absence of purposeful response to physical and verbal stimulation
- Loss of protective airways reflexes
- Inability to maintain patent airway
- Hypoxemia/hypercarbia
- Cardiovascular instability (arrhythmia or hypotension)

Table 5 American Society of Anesthesiologists (ASA) classification of preoperative or pre-procedure risk

P1	Normal healthy patient
P2	Mild systemic disease
P3	Severe systemic disease
P4	Severe systemic disease that is a constant threat to life
P5	Moribund patient not expected to survive without the procedure
P6	Brain dead patient whose organs are being considered for organ donation

Table 2 Depth of sedation

	Responsiveness	Airway	Spontaneous ventilation	Cardiovascular function
Minimal	Normal to verbal stimulation	Unaffected	Unaffected	Unaffected
Moderate	Purposeful response to verbal or tactile stimulation	No intervention required	Adequate	Usually maintained
Deep	Purposeful response after repeated or painful stimulation	Intervention may be required	May be inadequate	Usually maintained
General anesthetic	Unrousable even with painful stimulation	Intervention often required	Frequently inadequate	May be impaired

had a higher endoscopist rating for overall difficulty and retching during the procedure compared with the pharyngeal anesthesia group. Another study showed that performing endoscopic ultrasound without sedation, while less well tolerated, did not lead to longer procedure times, higher risks or increased reluctance to undergo a repeat procedure.[12] In this study, however, there was no control group—only blinded (to both patients and endoscopists) sedation and placebo groups. More recently, male sex, previous colonic resection, a high body mass index (BMI) and the absence of gynecological surgery were shown to be associated with higher colonoscopy completion rates in unsedated patients.[13]

Hypnosis has also been used to facilitate endoscopy.[14] Compared with intravenous midazolam, however, its use was associated with greater patient discomfort (as assessed by the patient) and less amnesia for the procedure. There was also a trend towards its being associated with greater technical difficulty on the part of the endoscopist. However, use of hypnosis led to less patient agitation as assessed by independent observers compared with both patients receiving pharyngeal spray without intravenous sedation and those receiving midazolam.

Local anesthetic application to the pharynx

The use of pharyngeal local anesthetic sprays as a prelude to endoscopy is widespread, although only a few studies have evaluated their efficacy. A recent meta-analysis[15] of five randomized controlled trials comprising 500 patients showed that the use of pharyngeal spray led to less procedure-related discomfort and less technical difficulty as rated by the endoscopist. Whether it also leads to a reduction in intravenous sedation requirements is not clear. There is a small risk of methemoglobinemia,[16] particularly with benzocaine, and some evidence that aspiration may be more likely to occur following pharyngeal spraying with local anesthetics.[17]

Music before and during the procedure

A recent meta-analysis of six prospective, randomized, controlled trials, found that listening to music before the procedure was associated with lower doses of analgesia and shorter procedure times.[18] Anxiety levels were also lower in the 'music' group, and there was a trend towards a reduced level of sedative agents but this did not achieve statistical significance.

Consent for intravenous sedation

Patients undergoing endoscopy should be fully informed of the risks of intravenous sedation in a preoperative consultation setting. Written information should be made available and there should be opportunity to ask questions. No separate consent process is required but issues surrounding sedation should be addressed in the same way as procedure-related risks and benefits before written consent is obtained.[19] Attempts to improve understanding of the procedure(s) by showing a video in fact may heighten anxiety levels and lead to the administration of higher doses of analgesia particularly in female patients.[20]

Pre-procedure assessment

Important predictors of adverse sedation events, which should be sought during the history and examination before the procedure, are outlined in Table 6.

Classification according to the ASA classification (Table 5) can be useful in risk stratification.

Special clinical situations

Endoscopy post-myocardial infarction

In a study of 135 patients, undergoing endoscopy less than one month following a myocardial infarction (MI),[21] the risk of major cardiopulmonary complications was 1.5%. Performance of endoscopic procedures on the day of the MI was found to be a significant risk factor for a procedure-related complication. In another study of patients, undergoing upper gastrointestinal endoscopy,

Table 6 Important issues in the pre-procedure assessment of patients undergoing endoscopy

History
1 Significant cardiac or respiratory disease
2 Neurological diseases, including previous stroke, transient cerebral ischemic attack or seizures
3 Obesity and obstructive sleep apnea and other conditions affecting the airway such as previous oropharyngeal surgery
4 History of snoring or noisy breathing suggestive of stridor
5 Adverse reaction to medications used in sedation and anesthesia
6 Use of medications, herbal therapies and recreational drugs
7 Alcohol and tobacco use
8 The length of time the patient has been fasted
9 Whether the patient could be or is in fact pregnant
Examination
1 Weight/estimation of body mass index
2 Resting blood pressure, pulse rate and respiratory rate
3 Auscultatory findings in the lung fields and over the precordium
4 Physical features in the neck and oral cavity that may make positive pressure ventilation more difficult. The Mallampati score (Fig. 1) is an indicator of the degree of difficulty of endotracheal intubation.

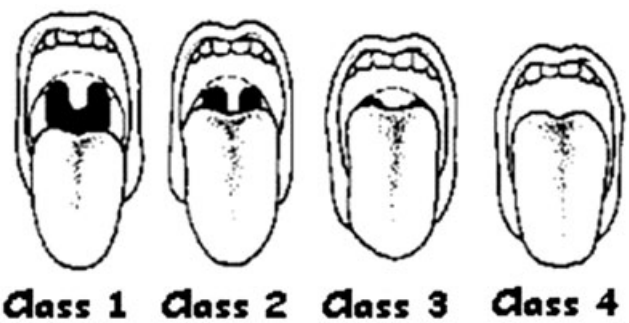

Figure 1 Mallampati classes. Class 1: Soft palate, uvula, fauces, pillars visible (no difficulty with intubation). Class 2: Soft palate, uvula, fauces visible (no difficulty with intubation). Class 3: Soft palate, base of uvula visible (moderate difficulty with intubation). Class 4: Only hard palate visible (severe difficulty with intubation).

who had had a MI in the previous 30 days,[22] an APACHE score of 16 or over was associated with a major complication rate of 21%, compared with 2% in those with lower APACHE scores. Hypotension in the period before the procedure was also an independent risk factor for the development of complications. Colonoscopy after MI is associated with a higher rate of minor cardiovascular complications compared with controls.[23] Endoscopic investigations should thus be avoided, if possible, in the first month, and particularly in the first day after an MI.

Implanted cardiac defibrillators

Small studies of fewer than 100 patients have not demonstrated any electromagnetic interference in patients with implanted cardiac defibrillators as a result of electrocautery use during endoscopy.[24,25] Avoiding potential interference of this nature can be readily achieved by placing magnets over these devices; this can be done after consultation with appropriate cardiology colleagues.

Endoscopy during pregnancy and lactation

Small, retrospective studies of pregnant women have indicated that administration of intravenous sedation during both upper and lower gastrointestinal endoscopy does not compromise maternal or fetal outcome in pregnancy, nor is it associated with congenital abnormalities.[26,27] Notwithstanding this, endoscopy should be avoided in pregnancy if possible, particularly in the first trimester where there is the potential for teratogenicity. There should also be a lower threshold to use anesthetic assistance particularly in emergency situations.

In patients in the latter stages of pregnancy there should be a reluctance to turn the patient into the supine position in view of the potential of the gravid uterus to compress the aorta and inferior vena cava. The commonly administered benzodiazepines (midazolam and diazepam), fentanyl and propofol are all classified as Australian Drug Evaluation Committee category C—'drugs which owing to their pharmaceutical effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.'[28] With respect to lactating women, data are limited. It is recommended that patients given midazolam should not breast-feed for at least 4 h after its administration. The lockout time after propofol is not clear, although it is likely to be longer in view of the fact that its maximal concentration in breast milk occurs between 4 and 5 h after administration. Thus, the 'pump and dump' approach to breast-feeding where breast milk is expressed and discarded for several hours before resuming breast-feeding seems reasonable. Fentanyl administration is not considered a contraindication to breast-feeding.[29]

Endoscopy in pediatric practice

In children the tongue fills up the upper airway to a greater extent than in adults, while enlarged tonsils and adenoids can further compromise the airway. In addition, the relatively higher oxygen consumption of children and the higher surface to volume ratio make the development of clinically significant hypoxemia, dehydration and hypothermia more likely in this group if appropriate preventative strategies are not in place. Endoscopy in children is thus almost always done under general anesthetic with endotracheal intubation. This is particularly the case in children younger than 10 years of age. Various ways of reducing separation anxiety and enhancing ease of intravenous insertion have been developed, including pre-procedure oral administration of midazolam (0.5 mg/kg),[30] and special psychological preparation.[31]

Other special situations that may impact on sedation practice

Chronic use of narcotics or benzodiazepines has been associated with greater meperidine (pethidine) and midazolam requirements for ERCP.[32] Young age, female sex, higher income and education levels and pre-procedure anxiety have been shown to predict patient dissatisfaction with sedation. A long procedure time and a difficult procedure also led to patient dissatisfaction.[33,34] A Korean study confirmed these findings,[35] but also showed that slender patients, who had not had previous endoscopic procedures were more likely to be alert and to experience pain during the procedure. Pena *et al.*[36] have shown that chronic use of psychotropic drugs and alcohol lead to greater levels of patient dissatisfaction. A recent US study showed that in ASA I and II patients, age over 60 and raised BMI were associated with the development of hypoxemia during endoscopy.[37]

Long procedures

There is evidence that longer procedures are associated with a higher risk of cardiorespiratory complications, particularly in patients over 65 years of age.[8] Engaging the assistance of a specialist anesthetist should be considered if it is anticipated that a procedure will last for more than half an hour.

Recent general anesthetic

If administration of sedative agents, particularly a general anesthetic, has occurred within the previous 24 h, special care should be taken as levels of anesthetic agents and their active metabolites may still be significant.

Emergency equipment and drugs

In view of the cardiorespiratory changes induced by the drugs used before and during endoscopy, appropriate resuscitation equipment should be easily accessible as outlined in Table 7.

Table 7 Resuscitation equipment that should be accessible in the endoscopy suite

1	Oral airways and nasal airways of various sizes
2	Endotracheal tubes
3	Laryngoscope handles, blades and stylets
4	Laryngeal masks
5	Ambu bag for intermittent positive pressure ventilation ('bagging and masking')
6	A range of intravenous catheters and isotonic fluids
7	Reversal agents including naloxone and flumazenil
8	'Crash trolley' with defibrillator and appropriate drugs for intravenous administration as part of advanced life support

Physical environment of endoscopy room

The room where endoscopic procedures are carried out should be large enough to accommodate appropriate endoscopic and monitoring equipment, and to allow the easy movement of attending health care workers within the endoscopy suite. Infection control measures, in particular disposal of blood contaminated equipment ('sharps') should be in conformity with the guidelines enunciated by the US Center for Disease Control. Facilities to house a variety of syringes, needles of different sizes, tapes, dressings, topical antiseptic agents, intravenous cannulas, intravenous tubing, giving sets and disposable gloves of various sizes should be present. Suction and oxygen outlets with appropriate tubing and accessories should be present. Patients should be positioned on trolleys of appropriate width with functioning side rails. Although endoscopy suites are often free standing, particularly in private practice, there is merit in having endoscopy suites either co-located or within easy access time to operating theaters, intensive care units and cardiac resuscitation teams.

Monitoring during intravenous sedation

Careful monitoring of patients is essential for the safe practice of endoscopy in sedated patients. Patients should be under constant clinical surveillance with particular attention to respiratory movement and response to verbal and tactile stimuli. At least one of the endoscopy suite personnel should be exclusively attending to the sedation and monitoring of the patient. This can either be a medical practitioner trained in sedation and monitoring, or a nurse working under the supervision of the medical or surgical endoscopist. In addition, continuous pulse oximetry and regular blood pressure and pulse measurements before, during and after the procedure(s) should be carried out, and the results recorded contemporaneously. Other monitoring techniques, such as capnography may be appropriate particularly in higher risk patients—this has been shown to be a more sensitive indicator of hypoventilation than either oximetry or visual inspection[38,39] and to reduce the risk of desaturation if used during ERCP and endoscopic ultrasound (EUS).[40] Electroencephalographic monitoring has not been shown to offer benefit in the context of endoscopic sedation; its use remains experimental.[41]

Oral pre-medication before endoscopic procedures

A double-blind randomized study from Hong Kong showed that oral administration of 7.5 mg midazolam 20 min before upper gastrointestinal endoscopy reduced patient anxiety and increased patient satisfaction.[42] Similar results were reported with premedication before sigmoidoscopy.[43] On the other hand, a German study failed to show any benefit from oral administration of 1 mg lorazepam before ERCP, and premedicated patients actually required higher doses of propofol in the early stages of the procedures and higher overall doses of ketamine compared with controls.[44] In general, for endoscopic practice it is unlikely that oral premedication adds substantially to smoother or safer sedation.

Intravenous drugs used for endoscopy

A variety of different drugs have been used and there is significant variation around the world. In general, three different agents/classes of agent are used—narcotics, benzodiazepines and propofol. In a recent survey of Australian anesthetists,[45] propofol use was virtually universal for endoscopic sedation and a majority of respondents used both fentanyl and midazolam. Most of the anesthetists who were surveyed administered propofol sedation in private clinics and private hospitals, although there has been an increasing use of anesthetist-administered propofol in public hospitals. These findings were similar to those reported by Clarke *et al.*,[46] also from Australia, with each of these drugs being given by general practitioner sedationists in over 97% of cases.

Narcotic analgesics

In Australia, fentanyl is the narcotic used most commonly,[45,46] and there is also significant use of pethidine. A group from London has shown a shorter recovery period for patients undergoing endoscopy if fentanyl and midazolam are used compared with the use of pethidine and midazolam, and there was no difference in pain perception.[47] Fentanyl is a synthetic opioid with a rapid onset and short duration of action. The half life is 2–7 h; this variation stems largely from differences in redistribution into adipose tissues and is independent of renal function. Fentanyl metabolites are not active and true allergy to it is very rare. These properties make it suitable for use in procedures of short duration. As with other opiates, it can lead to respiratory depression and hypotension. Hypovolemic patients and those with reduced respiratory reserve are particularly at risk of developing these complications.[48] In the elderly and frail and those with high ASA status, the dose of fentanyl should be reduced or opiate analgesia not used. Adult doses typically range from 25 μg to 100 μg (0.35–1.4 μg/kg). Naloxone, which competitively binds to μ-opioid receptors, is a reversal agent, the administration of which may be required to prevent or attenuate the above complications. Repeated administration may be necessary.

Benzodiazepines

Benzodiazepines are also used very frequently for endoscopy throughout the world. They have amnestic, sedative and anxiolytic properties in addition to their well-known anticonvulsant and muscle relaxant effects. These actions are thought to be mediated by attachment to gamma-amino butyric acid (GABA) receptors in the central nervous system. Its anxiolytic and muscle relaxant properties are not only mediated through GABA receptors but also through glycine receptors in the spinal cord.[49,50] Respiratory depression, which is probably related to a direct effect on the respiratory centre in the brain stem, leading to hypoventilation is an important adverse effect. Cardiovascular compromise with diminished cardiac output and peripheral resistance leading to hypotension, usually does not occur unless administration occurs during deep sedation.[48]

In Australia and throughout much of the world, midazolam is the benzodiazepine most commonly used for endoscopic sedation. Doses for adults undergoing endoscopy typically range from 1 to 5 mg (0.015–0.07 mg/kg). As with fentanyl, midazolam is

lipophilic, distributing quickly to the central nervous system shortly after intravenous administration. It has a rapid onset of action, usually inducing hypnosis within a few minutes. The redistribution half life is between 1 and 2.8 h in normal patients so that sedative effects wear off substantially within 2 h. The duration of action of midazolam is greater in the elderly. Factors that potentiate the effects of midazolam and its pharmacologically active metabolites include hypoalbuminemia, advanced age, diminished liver function and concomitant use of drugs that inhibit the hepatic cytochrome P4503A4 (CYP3A4) hepatic enzyme such as azole antifungals, human immunodeficiency virus protease inhibitors, diltiazem and phenytoin.[48] In chronic renal failure, there is a higher free fraction of midazolam although free drug clearance is the same as in controls.[51] This suggests that it may not be necessary to reduce the dose of midazolam if only one aliquot is administered. However, if further doses are given, the frequency with which this occurs should be reduced compared with that in patients without significant renal impairment. A paradoxical response to midazolam, where excitement rather than sedation is induced, has been described;[52] it is probably more common in the elderly.[48] The pharmacological effects of midazolam can be reversed by administration of flumazenil, which competitively blocks GABA receptors.

Propofol

Propofol (2,6-diisopropylphenol) is a more potent sedative agent with a narrower therapeutic window than the benzodizepines. It is also a lipophilic agent that acts on a different subset of GABA receptors from those which mediate the effects of benzodiazepines.[48] Because propofol is formulated with soy oil and egg lecithin, it is contraindicated in those with allergies to eggs or soybean. Propofol interacts with glycine, nicotinic and muscarinic receptors and has a direct effect on neural ion channels.[53] Propofol has a high volume of distribution and moves into the central nervous system and tissues rapidly. It thus has a rapid onset of action with hypnosis occurring usually within 40 s (the time for one arm-brain circulation). The duration of action of propofol is also short with the first phase of elimination typically taking 2–3 min.[54] The disposition and metabolism of propofol are complex, as three phases of elimination have been described.[48] Propofol possesses relatively little analgesic effect, and its amnestic effect is less than that of midazolam. It does however, have mild anti-emetic effects. Local pain during injection occurs in 30% of patients during administration of propofol.[55] It can lead to a fall in systemic vascular resistance and cardiac contractility and consequent hypotension. Propofol can reduce cardiac output without a concomitant change in heart rate.[56–58] The hemodynamic effects of propofol have been shown to be potentiated by concomitant use of fentanyl.[59] Respiratory depression can also occur with propofol use. Slow administration of propofol boluses has not been shown to attenuate these cardiorespiratory effects although using propofol as an infusion may do this.

Propofol can also give rise to myoclonic jerks and convulsions; these are usually very transient and occur as the sedative effects of propofol are wearing off. Importantly, these side-effects are particularly noted after relatively small doses have been used. Metabolism of propofol is different in the elderly[60] and the dose should be reduced in these patients. Impaired cardiac function also potentiates the effects of propofol but impairment in renal or hepatic function does not do this to a significant extent.[61] In patients with cirrhosis, use of propofol for elective upper endoscopy does not precipitate encephalopathy.[62]

Other agents used in sedation for endoscopy

Other drugs used in endoscopy include barbiturates, ketamine, droperidol, haloperidol and various inhalational agents. For various reasons, none of these agents has found favor although droperidol is popular in the USA. For a fuller discussion the reader is referred to a recent review.[48]

Dosing and timing of drugs used for endoscopic sedation

Adequate sedation can be achieved in most patients with the intravenous administration of a narcotic and a benzodiazepine, but there is a group of patients, who experience suboptimal sedation with this approach.[34] There is evidence that propofol administration offers a better quality of sedation without compromising safety.[63,64] For patients undergoing repeat endoscopic procedures, the regimen of sedative medication used previously may be a valuable guide to the choice and doses of medications selected with subsequent procedures.

There are generally two approaches to propofol administration.

1. 'Combination' regimens where a benzodiazepine and opiate are given intravenously (the opiate may be omitted in some patients such as the frail and elderly). After a pause, propofol is administered as an infusion or as incremental doses.
2. Propofol alone is administered either as an infusion or as incremental doses.

If the 'combination' approach is used, the doses of fentanyl and midazolam are generally less than would be used if there is no plan to use propofol. Increments of more than 30 mg of propofol should generally not be administered if midazolam and fentanyl have been given already. In addition, once propofol use has commenced, no further fentanyl or midazolam should be given. With respect to the combination approach, an Australian study reported median total doses of 4 mg midazolam, 75 μg of fentanyl and 60 mg of propofol in a sample of 500 cases drawn from 28 472 ambulatory patients undergoing endoscopy.[37] In virtually all patients, all three drugs were administered. In a Swiss study involving 27 061 ambulatory patients where propofol alone was used,[65] an initial dose of 0.5 mg/kg was used or 0.25 mg/kg in ASA III patients and those over 70 years of age; increments of 10–20 mg of propofol were given thereafter. VanNatta and Rex from Indiana compared four sedation regimens in a group of outpatients undergoing colonoscopy.[66] In each group the propofol dose was titrated according to sedation requirements: (i) propofol alone; (ii) fentanyl (50 μg with an optional further 25 μg being given subsequently for pain at the discretion of the endoscopist) and propofol; (iii) midazolam (1 mg) and propofol and (iv) all three of fentanyl (50 μg), midazolam (1 mg) and propofol. Where combination sedation was used, in each case, propofol was administered last. Those receiving propofol alone had the deepest sedation scores and received on average 215 mg of the drug compared with 82.5 mg in those receiving antecedent doses of both

midazolam and fentanyl. Propofol requirements in the other two groups were 140 mg (fentanyl alone group) and 125 mg (midazolam alone group). Those in the combination groups were discharged from hospital more quickly. Those in the fentanyl combination group remembered more pain associated with the procedure than those given propofol alone. This study is noteworthy for there being an almost 50% reduction in propofol requirements with only 1 mg of midazolam. Compared with the Australian study,[37] the doses of fentanyl and particularly midazolam were lower with correspondingly higher propofol requirements. Interpretation of the Indiana study must be guarded in view of the small numbers (200 patients in total).

Prevention and management of sedation-related complications

Careful administration of appropriately adjusted doses, particularly to the frail and the elderly, is essential if unwanted cardiorespiratory depression is to be avoided during endoscopy. There is evidence that supplemental oxygen reduces the risk of hypoxemia during colonoscopy,[67] although there are concerns that when supplemental oxygen is administered, oxygen saturation levels no longer reflect ventilatory function and may mask CO_2 retention.[68] Nonetheless, a recent Australian survey of anesthetists revealed that the use of supplemental oxygen was universal.[36] Expertise in managing airway obstruction and apnea is essential. Measures undertaken include chin lift, jaw thrust, placement of oral and nasal airway tubes, and for more prolonged periods of respiratory compromise, bag and mask ventilation. Reversal agents, including noloxone and flumazenil, are occasionally indicated. More advanced life support measures, including the use of laryngeal masks and endotracheal intubation are very rarely required in the ambulatory setting.[5]

For patients developing hypotension related to sedation agents, intravenous fluids may be indicated. For endoscopic procedures carried out in hospitals, ready access to a 'Medical Emergency' button is recommended.

Who should administer propofol-based sedation?

Traditionally, endoscopists have either given sedation themselves before and sometimes during procedures or have directed nursing staff to do this. In the USA, 'nurse-anesthetists' have also been deployed to give a highly selected range of medications to patients at low anesthetic risk using protocols that allow for variable patient sensitivity to intravenous agents. In the USA, the use of anesthetists for endoscopic sedation varies widely between states, ranging from less than 20% in the majority of states to over 50% in states such as New York and Florida.[69] Over recent years in Australia, particularly in the private sector, anesthetists have been called on to give sedation even to patients at low anesthetic risk. A recent survey of Australian anesthetists reported that endoscopy formed a significant part of the practices of most of the respondents.

Until recently only anesthetists were permitted to administer propofol and the impetus for increasing anesthetist involvement was to some extent to allow propofol use and thereby improve the quality of sedation without compromising safety. There is now evidence to indicate that propofol can be administered safely and efficaciously to patients in ASA grades I, II and III by non-anesthetists. In a series of almost 28 500 endoscopic cases, in which sedative medication was administered almost entirely by general practitioner sedationists,[37] there was no mortality and minimal morbidity. In a multi-centre study,[5] almost 650 000 patients who underwent propofol sedation, usually given as the sole agent, administered by a nurse under the direction of the endoscopist, there was only one anesthetic-related death. Whoever administers the sedation, there should be at least one appropriately trained individual whose sole function is to monitor the patient during the procedure; this person should also possess the skills required to take the necessary steps to prevent and manage sedation-related complications.

Notwithstanding the above, anesthetic assistance for endoscopic procedures is mandatory in many instances, particularly in elderly patients and those with higher ASA grading, or if there have been difficulties with intravenous sedation on a previous occasion. In addition, complex procedures, which are likely to be of long duration, should not be undertaken without anesthetic support. In this regard, a recent Australian study showed that many Australian teaching hospitals have made anesthetic support mandatory for ERCP.[70]

After care

Monitoring vital signs and conscious state after sedation is essential. Patients may pass into a deeper state of sedation after the procedure and may develop apnea and hypotension. The same resuscitation equipment, available during the endoscopy, should be readily accessible in the recovery area and personnel with appropriate skills in resuscitation should be available. Discharge is only appropriate when a patient has achieved a satisfactory level of conscious state with return to normal or near normal cardiorespiratory parameters (The Aldrete score[71]). Generally, patients recover to this level within 2 h, even after relatively long procedures due to the short duration of action of the administered agents. Nonetheless, it is important that written instructions be given to patients about the inadmissibility of driving and operating machinery for the next 24 h. Interestingly, recent Japanese experience suggests that it may be safe for patients to drive home after sedation for endoscopic procedures although doses used in that study were relatively small—most patients only received 40 mg of propofol as monotherapy.[72] Patients should be advised to avoid signing legal documents and should be accompanied by a responsible adult at the time of discharge.

The future

A number of new drugs have been developed that may be useful for endoscopic sedation. A water soluble prodrug of propofol, fospropopofol,[73] which has a lower peak yet a more sustained plasma level is being trialed. Dexmedetomidine is a new, reversible alpha agonist, associated with less respiratory depression than other sedative agents. Preliminary data suggest that it is just as safe as and possibly more efficacious than midazolam in the endoscopic setting in terms of side-effects and that it ranks highly for patient and endoscopist satisfaction.[74]

A number of different delivery systems have also been developed. These include patient-controlled sedation,[75] target-controlled infusions,[76] where drugs are delivered according to

computer-generated pharmacokinetic models, and computer-assisted personalized sedation (CAPS),[77] where propofol dosing is adjusted by a computer according to continuous physiologic monitoring. Data on the use of these approaches are preliminary.

Concluding remarks

There is no doubt that, worldwide, the ground is shifting in terms of who should administer propofol-based sedation for gastrointestinal endoscopy. Nurse-administered propofol (NAPS) is becoming a popular option in the USA and Switzerland, and NAPS use is likely to expand. The Australian and New Zealand College of Anaesthetists have recognized that propofol may be safely administered by non-anesthetists and in conjunction with the Gastroenterological Society of Australia and the Royal Australasian College of Surgeons this tripartite group has promulgated an important set of guidelines for its safe administration[3] (ref PS9). The document emphasizes the need for adequate training, certification and credentialing in sedation by non-anesthetists. The guidelines accept that in patients with ASA grades I–III, propofol may be safely administered by a medical practitioner, who is neither an anesthetist nor the endoscopist doing the procedure, and the tripartite group are in the process of establishing a suitable training program for endoscopists involving the use of didactic lectures, small group discussions, anesthetic simulators and observation sessions in units already using propofol in this way.

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Appendix

Summary of key points and recommendations regarding sedation for endoscopy

1 Although endoscopy without intravenous sedation is not recommended as a routine practice, it is a viable option in selected patients. Limited data suggest that pharyngeal spraying with local anesthetic sedation and pre-procedure music may facilitate endoscopy. Pre-procedure music may also reduce required quantities of intravenously administered drugs.

2 Pre-procedure assessment of the fitness of patients undergoing endoscopy with sedation is essential. Cardiovascular, respiratory and neurological co-morbidities should be assessed and a knowledge of allergies and reactions to drugs and sedative agents, smoking history, alcohol intake and medication use should be acquired. Those administering sedative agents and monitoring their effects should be aware of the nature of the proposed procedure and in particular its likely duration and potential complications.

3 Intravenous sedation for endoscopy should only be administered where there is adequate space to permit easy movement of personnel and equipment. Patients undergoing intravenous sedation for endoscopy should be monitored clinically and with pulse oximetry and regular blood pressure determinations. There should be ready access to intravenous reversal agents and intravenous fluids. All patients should have an intravenous cannula in place. The full range of equipment and drugs used in advanced life support should be readily available.

4 Sedation for endoscopy with propofol leads to better quality sedation without compromising safety. Propofol can be administered safely by non-anesthetists in selected patients undergoing endoscopic procedures. For endoscopic procedures where there is significant likelihood of airway obstruction and for those patients with high American Society of Anesthesiologists (ASA) grades, assistance from a specialist anesthetist is advisable particularly if it is anticipated that the procedure will be of long duration or endoscopically exacting. Such assistance may also be advisable if there have been difficulties with intravenous sedation on a previous occasion.

5 Due to their pharamacological profiles, midazolam, fentanyl and propofol are among the most commonly used drugs for intravenous sedation for endoscopy. If sedation is being administered by non-anesthetists, total doses of midazolam and fentanyl in general should not exceed 5 mg and 100 μg, respectively. If propofol is used following midazolam/fentanyl use, it should become the sole intravenous agent for the rest of the procedure(s) and generally should not be given in aliquots of more than 30 mg with 10 or 20 mg aliquots often being preferred in elderly and frail patients. Lower doses of propofol and fentanyl are given if it is anticipated that propofol is to be used. Time should be allowed for each aliquot of propofol to have its sedative effect before a further aliquot is administered. Alternatively propofol may be administered as an infusion.