The Dawning of a New Sedative: Propofol in Gastrointestinal Endoscopy

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Key Words

Propofol · Nurse-administered sedation · Patient-administered sedation

Abstract

Background: Using gentler endoscopes and improved sedation, great strides have been made in enhancing patients' comfort and acceptance of endoscopic procedures. Because morbidity and mortality have been associated with benzodiazepines in endoscopic sedation, safer alternatives were sought. Propofol (2,6-diisopropylphenol), a rapid and short-acting anesthetic, initially used in the 1980's for general anesthesia induction and maintenance, is a promising candidate. **Methods:** This review article examines experiences and literature references of propofol's use in endoscopic procedures. Three critical questions are posed: What are the major advantages and potential risks of propofol? When should propofol be used? Who should administer propofol, how should it be administered, and what type of monitoring is required? **Results:** With considerable inter-patient variability, the propofol dose must be carefully titrated according to the individual patient's response. Factors influencing dosage include age, ASA class, patient's height and procedure duration. Propofol's primary risk is its narrow therapeutic range which necessitates careful

patient monitoring. **Conclusions:** Propofol's advantages over benzodiazepines and narcotics include a more rapid onset of action, full relief of discomfort and rapid recovery to alertness without residual sedative effects or anterograde amnesia, thereby making this drug a cost-effective and, with proper monitoring, safe choice.

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Introduction

Role of Sedation for Endoscopy

The development of flexible fiberoptic endoscopes was a considerable step forward in the direct visual investigation of the body's interior without compromising its integrity. Nevertheless, for most patients, endoscopy remained an unpleasant experience that launched two major directions of further clinical developments: (1) The invention of smaller, smoother and more sophisticated instruments that enhance the procedure's tolerability [1], and (2) the introduction of, and improvement in, conscious sedation. Both developments are strongly correlated with the expanding frontiers of newer interventional techniques [2].

Although many clinical trials have documented the feasibility of endoscopies without any sedation [3–5], and reduction of cardiac stress under sedation does not seem to be a strong argument [6, 7], given the choice, a majority

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of patients would undoubtedly prefer sedation [8]. Patients' opinions probably depend not solely on their own personal experiences: the (poor) reputation of endoscopic procedures and patients' fears have become a consideration in public health viz. the predicted need for screening colonoscopies [9]. Finally, sedation should not be judged solely from the patient's perspective (i.e. making endoscopies more comfortable for patients), but also as a way of facilitating the procedure for the endoscopist, the latter being of increasing importance the more difficult the intervention [10].

Sedation with Benzodiazepines as Routine Practice

Several tragic deaths occurred when benzodiazepines were first being used. Nevertheless, since the 1980s, the use of benzodiazepines, often in combination with an analgesic, has become standard practice in the United States and many parts of Europe [11, 12]. However, even in the 1990s, a remarkable morbidity (1:200 to 1:2,000) and occasional mortality were still being reported with its use [13, 14].

Propofol

Besides the benzodiazepines, interest in another substance for endoscopic sedation has increased during the past few years: propofol [15]. With growing evidence supporting its use in both adults and children [16–23] propofol now stands at the threshold of a broad introduction into the endoscopy suite. Today, three major questions regarding its use have to be answered:

- What are the major advantages, and potential risks, of propofol?
- When should propofol be used?
- Who should administer propofol and how?

Advantages and Potential Risks of the Drug

Pharmacokinetics

Propofol (2,6-diisopropylphenol) is a rapid and short-acting anesthetic that came into use in the late 1980s. For quite some time, it was primarily used for the induction and maintenance of general anesthesia [24]. Its high lipid solubility results in a very fast onset of action (30–60 s) [25]. Following an initial bolus of propofol, the effect is terminated by a rapid redistribution of the substance to less well-perfused tissues and prompt hepatic conjugation. Nevertheless, a largely extrahepatic clearance without active metabolites exists making the substance also suitable for patients with liver disease [26]. Accordingly,

the plasma half life ($t_{1/2}$ distribution) is very short with 1.3–4.1 min (compared with 30 min for midazolam). This results in a rapid decline of propofol concentrations to levels below those required for hypnosis, and permits a rapid awakening even after prolonged administration [24]. The pharmacokinetics of propofol permit it to be given intravenously, either in bolus doses (usually in increments of 10–20 mg, depending on the clinical effect), or by continuous infusion with which different levels of sedation can be easily achieved with a change in dose [22]. The clinical applications of propofol have expanded within the past few years, and now include sedation in intensive care units and for outpatient procedures [27–29]. The exact mechanism of action of the drug is unclear, but, as with other CNS depressants, propofol may act on GABA receptors [24]. Propofol has good amnesic, but only minimal analgesic, properties and is often combined with an analgesic. It does not seem to markedly interfere with gastrointestinal motility [30]. With considerable inter-patient variability, the dosage has to be carefully titrated according to the individual patient's clinical state.

Age is one central determinant of the dosage required, and must be substantially reduced with increasing age [31] (cf. fig. 1). Other independent parameters that influence the dosage include ASA class (cf. table 1), the patient's height and the duration of the procedure [20, 32].

The advantages of propofol compared to benzodiazepines and narcotics are directly related to its properties: a more rapid onset of action, full relief from discomfort and rapid recovery to alertness without residual sedative effects or imponderable anterograde amnesia. As most endoscopy units are coming under increasing financial pressures, economic arguments for improved efficiency, e.g. faster patient discharge or reduction of procedure time, are important factors cited in the rationale for using propofol in routine endoscopy. Propofol patients also report a higher degree of satisfaction compared to benzodiazepine patients [9]. Propofol reduces costs in the recovery room and is associated with a more rapid return of patients to work or leisure [33].

Level of Sedation

Sedation is a continuum of progressive impairment in consciousness that has been roughly divided into four different levels, ranging from anxiolysis or minimal sedation to general anesthesia [34] (cf. table 2).

Although in the literature, the use of propofol is often associated with deep sedation, it is essential to note that the level of sedation is primarily dose dependent. Deep

sedation can also be achieved by administration of benzodiazepines, while small doses of propofol can lead solely to anxiolysis without any reduction in vigilance. When used as a single substance, the lacking analgesic effect may possibly lead endoscopists to aim for deeper levels of unconsciousness [9]. Nevertheless, propofol can be used to achieve a state of conscious sedation where communication is still possible.

Risks

The principal and most important risk of propofol use is its narrow therapeutic range. This poses the danger that

Table 1. ASA classes according to the American Society of Anesthesiologists

P1	normal healthy patient
P2	patient with mild systemic disease
P3	patient with severe systemic disease
P4	patient with severe systemic disease that is a constant threat to life
P5	moribund patient, not expected to survive without the operation

Based on the American Society of Anaesthesiologists.

Fig. 1. Influence of age on propofol dose required, based on a prospective evaluation of 4,079 EGDs [according to 31]. Mean and SD.

Table 2. Continuum of sedation depth based on guidelines published by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists [34]

	Minimal sedation (anxiolysis)	Moderate sedation/analgesia (conscious sedation)	Deep sedation/analgesia	General anesthesia
Responsiveness	normal response to verbal stimulation	purposeful ¹ response to verbal or tactile stimulation	purposeful ¹ response after repeated or painful stimulation	unarousable, even with painful stimulus
Airway	unaffected	no intervention required	intervention may be required	intervention often required
Spontaneous ventilation	unaffected	adequate	may be inadequate	frequently inadequate
Cardiovascular function	unaffected	usually maintained	usually maintained	may be impaired

¹ Reflex withdrawal from painful stimulus is not considered a purposeful response.

patients might unintentionally slip into a state of deep sedation – or even anesthesia – with concomitant impairment of spontaneous ventilation. In contrast to benzodiazepines, no reversal agent, such as flumazenil (Anexate®), is available, and patient resuscitation must be carried out using the jaw thrust maneuver, positioning of a nasopharyngeal tube or even positive pressure bag ventilation. Due to the short duration of action, this intervention is fortunately required for only a few minutes. Nevertheless, endoscopists must be aware of this potential danger and alert for any prolonged period of apnea [35]. This risk necessitates that those who administer propofol must have training in advanced cardiac life support (ACLS) and airway management. Indeed, in some countries, propofol's use is restricted solely to the anesthesiologist [9].

One rarely-cited benefit regarding propofol's safety is that the major negative effects of the drug develop concurrently with when the most attention is being focused on the patient. Therefore, any alterations in physiologic parameters can be detected immediately. This stands in contrast to benzodiazepines where active metabolites may have their largest effect after cessation of the endoscopic procedure [36].

Safety Compared to Midazolam

Three large prospective studies (involving 562 patients) compared propofol to midazolam (or midazolam in combination with meperidine) and found comparable levels of safety [16, 17, 37]. With regard to patient and/or endoscopist satisfaction, various studies have found propofol to be superior [16–18, 38]. However, it must be stated that the drug was not always used in the same fashion, thereby requiring a stratification of propofol use under different circumstances.

Drug Combinations

Anesthesiologists have proposed regimens in which propofol is combined with an analgesic and/or another sedative [24]. Due to the mentioned lack of analgesic properties, the combination with a pain-relieving drug is rational. Nevertheless, non-anesthesiologists should be extremely cautious of possible side effects since the drugs act synergistically and may cause a depression in ventilation [39]. A combination of propofol with an opioid always necessitates a reduction in the dosage [32]. A long-acting opioid (such as pethidine) can be administered in advance [32], but ideally, the profile of action of the administered drug should be comparable and not abolish the benefits of propofol. From this point of view, the com-

bination with a very short-acting (and highly potent) opioid, such as alfentanil, for example in a fixed ratio, would make sense for painful procedures [40].

The combination of propofol with a benzodiazepine has been primarily used to ensure deep sedation [41–43] or to reduce the required quantities of the rather expensive propofol [44]. Besides the problem of predicting possible side effects, this schedule obviously eliminates the essential advantage of propofol and therefore presents no improved benefit. The argument that, with benzodiazepines, at least one component should be capable of being neutralized in cases of emergency leads, in our opinion, to a false sense of security. The main thrust should be to prevent an emergency situation by cautious use as well as careful selection and monitoring of the patients.

When Should Propofol Be Used in GI Endoscopy?

Within the past few years, two different strategies have been developed for using propofol in GI endoscopy. First, by emphasizing its origin as an anesthetic agent and its potential to easily achieve deep sedation, some authors have suggested reserving propofol for prolonged and difficult endoscopic procedures, i.e. using the drug primarily for its superior hypnotic potency [17, 18, 45]. Using this strategy, propofol becomes a second-line drug that can replace the need for having an anesthesiologist, and is reserved for difficult procedures. This enables gastroenterologists to perform endoscopic interventions while patients are in a quiet state of (deep) sedation.

Underscoring its pharmacokinetic properties, other authors have introduced the substance as a routine first-line hypnotic for all EGD and colonoscopies, providing special benefits in an outpatient setting [22, 37, 46, 47]. With this view, its rapid re-awakening and metabolism are major benefits for the physician who strives for a level of sedation comparable to the benzodiazepines.

We employ propofol in the latter fashion as a routine substance for all types of endoscopic procedures, including painful rectoscopies and even liver biopsies.

EGD

For EGDs performed in outpatients, propofol may be the ideal substance [37, 48, 49], although the dosage needed to smoothly perform upper endoscopy may be slightly higher than for colonoscopies with an accompanying increased risk of apnea [9, 20]. Nevertheless, the short procedure time corresponds very well to the action of the drug. After an adequate level of sedation has been reached, propofol permits most EGDs to be performed without further incremental application of the drug while

still achieving a perfect amnesia. Patients are able to communicate immediately after the procedure and can be discharged after 20 min, although they should not be allowed to drive.

Colonoscopies

During colonoscopies, the level of sedation can be adjusted to the patient's need with a deeper level during passage of the sigmoid and a lower level during withdrawal [9]. As do most authors in these procedures, we likewise administer the drug using a bolus technique according to the specific patient's requirement. If applicable, patient-controlled sedation (see below) may be an ideal method for this type of procedure [40].

ERCP and EUS

For prolonged procedures, such as ERCP or EUS, a perfusion technique with an injection pump may be more convenient than the bolus technique [17, 45, 50]. The level of satisfaction cited by both the patient and the investigator are superior with propofol than with midazolam [45]. However, conflicting results have been reported from the scant experiences made to date when using a target-controlled infusion (TCI) technique. The need for a considerable titration time makes it unattractive for short procedures, and a high rate of oversedations in a pilot study is noteworthy [51–53].

Who Should Administer Propofol, How Should It Be Administered, and What Type of Monitoring Is Required?

Four methods of drug administration have been reported. These include propofol administered by: (1) an anaesthesiologist [45, 54]; (2) another physician (gastroenterologist) [17, 18, 50]; (3) a trained nurse [20, 55, 47], and (4) by the patient himself [40, 56]. In a recent study, the delivery of propofol by registered nurses has been shown to be more cost-effective than administration by an anaesthesiologist or by an additional physician [18]. It thus appears that the introduction of propofol into GI practice is linked to the documentation of its safety in the hands of non-anesthesiologists [39, 57, 58]. Experiences with nurse-administered propofol sedation, abbreviated NAPS, have been reported from different centers in the US and Europe. Together, the authors have examined more than 20,000 NAPSs that took place at two different institutions: a tertiary university hospital and a hospital-based private practice [20, 23]. The overall reported safety of NAPS is well comparable to other methods. In more than 50,000 sedations, there has been no observed mortal-

ity, no need of endotracheal intubation and the incidence of brief mask ventilation was between 1:500 and 1:1,000 [9, 19, 20, 23, 31, 32, 47, 55, 59].

Patient-Controlled Sedation (PCS)

The combination of propofol with an anesthetic agent has likewise been repeatedly shown as practical for PCS [40, 54, 56, 60, 61]. The typical self-administered bolus consists of 4.8 mg propofol and 125 µg alfentanil [40, 56]. All studies showed a perfect safety result with this form of application and a high degree of patient satisfaction. However, part of the concept of PCS is that patients have to react to an unpleasant sensation. Therefore, they often seem to be sedated only at a rather low level and may experience pain more often than do conventionally sedated patients. Although this method seems to provide an individually tailored and adequate sedation that would save on additional personnel resources, this technique may not be applicable in a significant portion of patients who are less than eager to take responsibility for their own sedation.

Monitoring

Several guidelines have defined the use of sedative drugs by non-anesthesiologists [34, 62–65]. As with any form of conscious sedation, pulse oximetry, nasal oxygen administration and repeated blood pressure measurement are mandatory. With the introduction of propofol, capnography has been suggested as an improved modality for monitoring respiratory activity and for detecting apnea at an earlier stage [35]. Nevertheless, end-tidal CO₂ measurement in respired air may provide inaccurate results, and transcutaneous CO₂ monitoring has therefore recently been proposed as an alternative for supervising ventilation [66].

Training

The crucial point in the debate over nurse-administered propofol sedation remains the specific knowledge and training requirements. It is generally claimed that every person involved in NAPS, nurses as well as endoscopists, should have experience and knowledge of both the theoretic basics of monitoring and pharmacology of the drugs used. In addition, they should be trained in practical ACLS procedures, including positive pressure ventilation with a bag valve system [9, 20, 33]. As NAPS is still in its beginnings, the introduction of NAPS should be embedded in a quality assurance program with defined protocols of drug administration and monitoring of the patients' reactions. In agreement with others, we would

emphasize the need of learning the practical administration of propofol with the support of an anaesthesiologist [9].

Conclusion

Propofol is a very promising substance that provides remarkable advantages over benzodiazepines for sedation in endoscopy. With its rapid onset and short duration of

action, various drug administration methods, including patient-controlled sedation, are practical. The safety profile is almost equal to that of the benzodiazepines and satisfaction reported by both the patient and endoscopist is much higher [33]. The large number of sedations carried out by registered endoscopy nurses confirm that this is also a safe form of application when cautious protocols are used and the nurses are adequately trained.

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