Is propofol the optimal sedative in gastrointestinal endoscopy?

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Abstract

Propofol is a sedative agent commonly used for sedation in gastrointestinal endoscopy. Its pharmacologic properties render propofol an almost ideal drug to achieve and maintain the targeted level of sedation in even complex gastrointestinal procedures. When compared with other sedative agents, propofol is associated with better patient and endoscopist satisfaction and shorter recovery times. Furthermore, propofol can be combined with other sedatives to reduce the total dosage required to achieve the targeted sedation. Its safety is demonstrated by multiple studies, in which adverse events occurred very rarely. Nevertheless, the use of propofol by non-anesthesiologists is illegal in many countries and in those permitted, a structured curriculum with clinical training must first be successfully completed. However, various studies have shown that non-anesthesiologist administration of propofol is comparable in efficacy and safety to administration by an anesthesiologist and more cost-effective. The results of numerous studies indicate that propofol is superior in many aspects compared with traditional sedative agents. (Acta gastroenterol. belg., **2018,** 81, **520-524**).

Key words : propofol ; sedation ; endoscopy ; anesthesiologist ; safety ; efficacy.

Introduction

The performance of various gastrointestinal procedures under sedation is the norm nowadays. The use of sedation has been associated with higher patient satisfaction and better procedural quality, leading to increasing demand for sedation by the patients. The main concerns about the use of sedation in endoscopy are the higher procedural cost, the increase in patient recovery time, the potential risk for complications after administering a sedative drug and whether the presence of an anesthesiologist is mandatory (1). Numerous studies and discussions have been conducted so far to find the optimal strategy for sedation during endoscopy.

The most common pharmacological agents used to achieve a moderate level of sedation during gastrointestinal endoscopy are propofol, midazolam, fentanyl and meperidine (2). Propofol appears to have several advantages when compared with other sedative agents, since it is both safe and effective for all gastrointestinal endoscopy procedures and appears to have faster recovery times, better sedation level, greater patient cooperation and similar or lower risk for complications (3).

The aim of the present mini-review is to summarize the current knowledge on the use of propofol in gastrointestinal endoscopy.

Pharmacology

Propofol (2,6-diisopropylphenol) is a phenolic derivative with satisfactory sedative, hypnotic, antiemetic and amnesic properties and also with minimal analgesic action. It is a highly lipophilic agent that can easily cross the blood-brain barrier and as a result has a rapid onset of action (< 1 min). Propofol is fast redistributed into peripheral tissues leading to a short duration of action (approximately 4-8 min) whereas recovery occurs within 10-20 min after discontinuation of administration. Propofol is metabolized in the liver and excreted by the kidneys. Several factors significantly affect its pharmacokinetic profile and clinical effects, particularly age, gender and weight (4). The elderly are more sensitive to propofol due to decreased volume of distribution and total body clearance of propofol. On the other hand, chronic kidney disease or cirrhosis do not significantly alter the pharmacokinetics of propofol (1).

The depth of sedation with propofol increases in a dose-dependent manner. Propofol can be used alone or in combination with other sedative drugs, including midazolam and fentanyl. When used alone, it can be administered either as bolus injection or as continuous infusion. The preferred method is the bolus infusion of an initial dose of 10-60 mg, followed by additional doses of 10-20 mg with a minimum interval of 20 to 30 sec between the doses. When combined with other sedatives, a pre-induction dose of either an opioid (25 to 75 μg of fentanyl or 25 to 50 mg of meperidine) or 0.5-2.5 mg of midazolam or both are administered. Propofol is then administered at an initial bolus dose of 10-40 mg or up to 0.5 mg/kg followed by additional doses of 5-20 mg to maintain the target level of sedation (1). Intermittent bolus application of propofol appears to have better recovery times and less frequent episodes of hypotension when compared with continuous infusion (5).

Administration of propofol is generally safe and is associated with few adverse effects. The major adverse effects are respiratory depression, dose-

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dependent hypotension and pain during injection. These complications typically respond rapidly to dose reduction or interruption of drug infusion. Currently, there is no pharmacologic antagonist of propofol. Propofol is contraindicated in patients with known allergy to soy protein and, depending on the propofol formulation, to eggs, peanuts, sulfites and others. It should also not be administered during pregnancy and breastfeeding.

Efficacy

Propofol has long been used in gastrointestinal endoscopy and its efficacy has been proven by many clinical studies. In a prospective, randomized, single-blinded study, 222 patients undergoing therapeutic esophagogastroduodenoscopy (EGD) or endoscopic retrograde cholangiopancreatography (ERCP) were divided into those who received balanced propofol sedation (BPS) i.e. propofol in combination with midazolam and meperidine and those who received conventional sedation (midazolam and meperidine). BPS provided higher healthcare provider satisfaction and better patient cooperation (6). In diagnostic EGD, propofol sedation also appears to be safe and practical. Indeed, in a study that involved 10,662 adults who received low-dose bolus propofol up to a maximum dose of 120 mg for diagnostic EGD, 99% of the patients were willing to repeat the same procedure again (7). In another study, 2,101 patients underwent colonoscopy as outpatients. Propofol was given for sedation up to a maximum dose of 200 mg and its effectiveness was assessed with the evaluation of full recovery at least 30 minutes after the procedure, questionnaires and phone contact within 2 weeks after the endoscopy. Again, 99% of the patients were willing to repeat the same procedure (8). Regarding the use of propofol in advanced endoscopic procedures such as ERCP, endoscopic ultrasonography (EUS) and deep small bowel enteroscopy, a meta-analysis of 9 prospective randomized trials with a total of 969 patients concluded that propofol is associated with shorter recovery time, improved patient cooperation and better sedation and amnesia (9). Clinical trials have also demonstrated the efficacy of propofol in endoscopic submucosal dissection (10,11).

Propofol appears to compare favorably with other sedatives. A meta-analysis of 22 randomized controlled trials (RCTs) involving 1,798 patients that compared propofol with traditional sedative agents concluded that propofol is safe and effective for gastrointestinal endoscopy procedures and is associated with shorter recovery and discharge periods, higher post-anesthesia recovery scores, better sedation and better patient cooperation than traditional sedation (3). Another meta-analysis of 22 RCTs reached similar conclusions regarding the efficacy of propofol in colonoscopy (12).

Propofol can also be combined with other sedative agents to achieve a synergistic sedative effect. Propofol monotherapy and propofol combined therapy were shown to have comparable efficacy in a recent meta-analysis of 22 RCTs that involved 2250 patients (13). However, the European Society of Gastrointestinal Endoscopy suggests propofol monotherapy with the exception of patients anticipated to be very anxious, during long-lasting procedures, patients with impaired left ventricular function or with previous pronounced hypotension following propofol administration and other particular situations (14), such as the elderly, who have greater sensitivity to propofol (15). The main advantage of combination sedation is a reduction in total propofol dosage but at the expense of slower post-procedure recovery (16). When deep sedation is required, combined sedation with propofol and fentanyl with or without midazolam (17) or meperidine (18) was shown to have better recovery times and comparable overall satisfaction.

Safety

The safety of propofol administration during endoscopy has been for a long time the main argument against its use. Several studies evaluated the safety of propofol use in endoscopy. A systematic review reported minimal complications and only 4 deaths in 646,080 endoscopic procedures (19). Similarly, in a prospective trial of 191,142 patients undergoing endoscopy, 82 sedation-related complications (0.00042%) and 6 sedation-related deaths (0.00003%) were recorded (20).

Additionally, many large studies compared the safety of propofol with other commonly used sedation regimens. A multi-center prospective study showed that propofol monotherapy had lower complication rates compared with midazolam and drug combinations (21). Multiple meta-analyses of RCTs showed that the use of propofol is associated with similar or lower complication rates compared to traditional sedation regimens, such as monotherapy or combinations of midazolam, fentanyl and meperidine (3,12,22). Several studies also examined the use of propofol in advanced endoscopic procedures including as ERCP showing similar complication rates with propofol and other sedation regimens (9,22). Furthermore, many studies investigating the use of propofol as a sedation agent in cirrhotic patients undergoing gastrointestinal endoscopy. A meta-analysis of 5 studies comparing propofol with midazolam showed that there was no significant difference in the rate of complications between the 2 regimens (23). Regarding the use of propofol in children undergoing gastrointestinal endoscopy, a recent meta-analysis of 11 RCTs comparing different sedation regimens concluded that propofol-based sedation is the best choice for gastrointestinal endoscopy in children (24).

Regarding the safety of propofol monotherapy versus propofol combined with other sedative agents, there is currently no conclusive evidence to indicate more favorable safety profile for any of these 2 regimens

(13,25), though propofol combination therapy has the advantage of using lower doses of propofol.

There have been many recommendations to further improve the safety of endoscopic procedures using propofol. The European Society of Gastrointestinal Endoscopy (ESGE) and the American Society of Gastrointestinal Endoscopy (ASGE) both issued guidelines, highlighting the steps that must be taken by endoscopists to ensure optimum safety for patients undergoing endoscopy under propofol (14,26). Both guidelines give special consideration to the relationship between the American Society of Anesthesiology (ASA) score and complication rates that has been observed in some studies (20,27), highlighting the need for specialist assistance in patients with high ASA scores. The use of capnography was also proposed in high-risk patients even though studies have not yet shown conclusive benefits from this method (28). Furthermore, both ESGE and American Scientific Societies (ASGE, American Gastroenterological Association, American College of Gastroenterology, American Society for the Study of Liver Disease and American Society of Gastroenterology Nurses and Associates) issued sedation training curriculums, in order to facilitate the training of gastroenterologists and other personnel participating in endoscopic procedures in the use of propofol-based endoscopic sedation (29,30).

Non-anesthesiologists administration of propofol

There is a continuous debate whether propofol should be allowed to be used by personnel without expertise in the field of anesthesia. The ESGE and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) published an updated guideline in 2015, which described the conditions needed to be met so that the administration of propofol by non-anesthesiologists is safe and feasible (14). According to these guidelines, the presence of an anesthesiologist is primarily required in patients with ASA score ≥ 3, with a Malampati's class ≥ 3 or with other conditions that place them at risk of airway obstruction, in patients who chronically receive narcotic analgesics and in cases where a long-lasting procedure is anticipated. However, this recommendation is graded as weak, with low quality of evidence. The ASGE also published guidelines for sedation and anesthesia in gastrointestinal endoscopy in 2018 (26). These guidelines agree with the ESGE guidelines regarding the cases where consultation with an anesthesiologist to provide sedation is mandatory. Both ESGE and ASGE state that the sedation team must be appropriately educated and trained in sedation regimens and at least one member should be trained in advanced life support. Constant monitoring of the patient with pulse oximetry, intermittent blood pressure measurement, electrocardiography and possibly capnography is obligatory. Administration of sedation and continuous monitoring of the patient must be assigned to a well-trained person dedicated to this purpose. There must also be readily available, age-appropriate equipment for airway management and resuscitation. The patient should fulfill minimum discharge criteria (the post-anesthetic discharge scoring system (PADSS) is suggested) before being discharged (14,26). Clinical trials confirmed that non-anesthesiologist administration of propofol (NAAP) is safe and effective in low-risk patients (31,32). In a clinical trial that evaluated the safety of NAAP, 277 low-risk patients scheduled for colonoscopy received either NAAP or anesthesia by an anesthesiologist. The trial concluded that NAAP is equivalent to anesthesiologist-administered sedation regarding the rate of adverse events (33). Considering the safety profile of endoscopist-directed administration of propofol (EDP), EDP is estimated to have economic benefit. A cost-effectiveness analysis estimated that $3.2 billion in the US and €0.8 billion in France could be saved over a period of 10 years, if EDP is implemented in a colorectal cancer screening setting (34).

Nevertheless, the use of propofol by non-anesthesiologists is not generally accepted and, in many countries, is considered to be illegal according to national legislation. In countries where NAAP is legal, a person needs to complete a structured curriculum with clinical training before being qualified to practice NAAP (30). The summary of product characteristics of propofol states that it should be given by those trained in anesthesia (or, where appropriate, doctors trained in the care of patients in intensive care)(35). FDA opposed in 2010 a Citizen Petition by the American College of Gastroenterology (ACG) asking for this statement to be removed. In 2011, 21 national societies of anesthesiology in Europe signed a Consensus Statement stating that due to its well-known risks, propofol should be administered only by those trained in the administration of general anesthesia (36).

Practice patterns

There are varying practice patterns regarding the use of propofol in gastrointestinal endoscopy in different countries. USA was among the first countries with documented use of propofol by endoscopists from the mid-2000s; in an early study, 26% of gastroenterologists used propofol for gastrointestinal endoscopy (37). A more recent study used database result from years 2000 to 2013, estimating propofol use in only 2.4 % of colonoscopies (38), although with a rising trend in the more recent years, reaching almost 20%. This figure is substantially lower than in other countries and this difference might be attributed to the projected growth of rate of anesthesia professional-delivered sedation for gastrointestinal endoscopy in the US (39) due the FDA restriction of the use of propofol to personnel trained in the delivery of general anesthesia. The need for anesthesiologist assistance increases the costs for both the gastroenterologist and the patient, limiting the use of propofol-based regimens.

On the contrary, propofol sedation has flourished in European countries and Canada, with nationwide surveys reporting rates of > 90 % of gastroenterologists using propofol for endoscopic sedation. Specifically, in Germany, Canada and Switzerland, propofol is used in the majority of gastrointestinal endoscopies either as a single agent or in combination with others (40-42). However, in countries such as Italy, Spain and Greece, propofol is underused, mainly due to being used primarily by an anesthesiologist and not by an endoscopist (43-45).

Conclusions

There is substantial amount of scientific data showing that propofol is more efficient and at least equally safe compared with other sedative agents. In addition, it has been shown that non-anesthesiologist administration of propofol is equally safe and more cost-effective than administration by anesthesiologists. Preference of other agents over propofol has been proven to be a product of medicolegal issues and specialty politics. Special considerations should be given for certain groups of patients but current evidence suggests that propofol might represent the optimal sedative in gastrointestinal endoscopy.

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