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REVIEW

Sedation in gastrointestinal endoscopy: Current issues

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Abstract

Diagnostic and therapeutic endoscopy can successfully be performed by applying moderate (conscious) sedation. Moderate sedation, using midazolam and an opioid, is the standard method of sedation, although propofol is increasingly being used in many countries because the satisfaction of endoscopists with propofol sedation is greater compared with their satisfaction with conventional sedation. Moreover, the use of propofol is currently preferred for the endoscopic sedation of patients with advanced liver disease due to its short biologic half-life and, consequently, its low risk of inducing hepatic encephalopathy. In the future, propofol could become the preferred sedation agent, especially for routine colonoscopy. Midazolam is the benzodiazepine of choice because of its shorter duration of action and better pharmacokinetic profile compared with diazepam. Among opioids, pethidine and fentanyl are the most popular. A number of other substances have been tested in several clinical trials with promising results. Among them, newer opioids, such as remifentanil, enable a faster recovery. The controversy regarding the administration of sedation by an endoscopist or an experienced nurse, as well as the optimal staffing of endoscopy units, continues to be a matter of discussion. Safe sedation in special clinical circumstances, such as in the cases of obese, pregnant, and elderly individuals, as well as patients with chronic lung, renal or liver disease, requires modification of the dose of the drugs used for sedation. In the great majority of patients, sedation under the supervision of a properly trained endoscopist remains the standard practice worldwide. In this review, an overview of the current knowledge concerning sedation during digestive endoscopy will be provided based on the data in the current literature.

Key words: Gastrointestinal endoscopy; Endoscopy; Sedation; Analgesia; Digestive system

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INTRODUCTION

Today, both the number and complexity of endoscopic procedures have increased considerably due to the wide availability and application of sedation, which facilitates successful endoscopic procedures because it can relieve patients' anxiety and discomfort, concurrently allowing them to experience a rapid recovery with the use of antidotes. Consequently, the willingness of patients to undergo endoscopy, irrespective of the severity of their situation, is increasing.

The best methods for analgesia and sedation during digestive endoscopy are still debated. Intravenous sedation can be administered by the endoscopist who concurrently performs the procedure while a qualified nurse monitors the patient's state of consciousness and vital signs. Providing an adequate regimen of sedation/analgesia may be considered a form of art, which influences,

for example, the quality of the examination and the patient's and physician's satisfaction with the sedation[1]. It must be argued that the optimal level of sedation differs according to the procedure being performed. Deep sedation or even general anaesthesia may be preferred for therapeutic procedures in which it is important for a patient to remain immobile. It is obvious that endoscopists commencing sedation/analgesia should be able to rescue patients whose level of sedation has become deeper than initially intended.

However, even today, many significant issues, such as the benefits, risks, and costs of sedation; the selection of the most suitable drug and combination of drugs for use; and the person responsible for the administration of sedation and monitoring of the patient, especially during time-consuming procedures such as colonoscopies and endoscopic retrograde cholangiopancreatography (ERCPs), remain unanswered[2].

The aim of this review is to provide the reader with an overview of the current knowledge concerning sedation during digestive endoscopy (drugs currently used and drugs under investigation, sedation during upper and lower gastrointestinal (GI) endoscopy and ERCP, and endoscopy in special situations) based on the data available in the current literature.

SEDATION PRACTICES

Sedation practices vary in different countries depending on health system regulations and local circumstances. On the other hand, differences in the setting in which the practice of gastroenterology and endoscopy takes place, e.g., at university hospitals versus community hospitals or private endoscopy units, as well as other systematic practice differences, could influence the attitude of endoscopists concerning sedation practices.

Data concerning the incidence of sedation application in routine practice are rather limited. Among the members of the Canadian Association of Gastroenterology, more than 90% use sedation during colonoscopy[3]. The use of sedation has become a standard practice during GI endoscopy in Italy[4]. Among the members of the Hellenic Society of Gastroenterology, 64% use sedation regularly in cases of upper GI endoscopy, 78% use sedation in colonoscopies, and 100% use sedation during ERCP and endoscopic ultrasound (EUS)[5]. In the United States, more than 98% of colonoscopies are performed with intravenous sedation[6]. In Switzerland, the use of sedation in GI endoscopy has markedly increased, and the use of electronic monitoring has become a standard practice. In this country and during 2003, sedation was used in 78% of upper and lower GI endoscopic procedures, compared with 60% in 1990. In Germany, the majority of esophagogastroduodenoscopy (EGDs; 74%) and colonoscopies (87%) are carried out under sedation[7]. In Spain, sedation is used in 20% of EGDs and 20% of colonoscopies, while ERCP is almost always performed under sedation[8].

With regard to the most common sedation regimen used in different countries, it was reported that most Canadian endoscopists use a combination of midazolam and fentanyl for colonoscopy, while propofol, either alone or in combination with other drugs, is used in a small proportion of patients[3]. Interestingly, a significantly higher proportion of adult gastroenterologists who routinely used propofol are highly satisfied compared with those using other drugs. According to a recent survey among the members of the Italian Society of Digestive Endoscopy, the most commonly employed sedation patterns are benzodiazepines for upper GI endoscopy (50.8%), benzodiazepines plus opioids for colonoscopy (39.5%) and enteroscopy (35.3%), and propofol for ERCP (42.3%) and EUS (35.6%). Concerning the use of propofol, 66% of endoscopists stated that the drug was administered exclusively by anaesthesiologists[4]. In Greece, 62.1% of the endoscopists use synergistic sedation (benzodiazepines plus opioids), 35.3% use benzodiazepines alone and 33.8% use propofol-based sedation in selected cases. Propofol administration is directed by an anaesthesiologist in most cases[5]. In the United States, more than 75% of endoscopists use a benzodiazepine plus narcotic combination, with the combination of midazolam and fentanyl being the most common[6]. In Switzerland, midazolam is the most commonly used medication. The drug is administered by the endoscopy nurse *via* an intravenous cannula. A significant percentage of endoscopists (43%) also use propofol regularly, mainly in a hospital setting. Endoscopists reporting the use of propofol without the assistance of an anaesthesiologist had performed a total of 82 620 procedures. The morbidity in this group of patients was 0.19%, with no cases of mortality[9]. The doses of midazolam and fentanyl used by the Canadian endoscopists are similar to those recommended in the United States (< 6 mg of midazolam and < 200 μg of fentanyl) and in the United Kingdom (< 5 mg of midazolam and < 100 μg of fentanyl)[10]. In Spain, the most common drugs were midazolam for gastroscopy and midazolam and pethidine for colonoscopy and ERCP, while propofol is most frequently used by anaesthesiologists[8]. In Germany, the most frequently used agents for sedation are midazolam (82%) and propofol (74%), and the most common sedation regimens used are propofol plus benzodiazepines (38%) and benzodiazepines plus an opioid (35%)[7].

In Italy, pulse oximetry is the most common system for patient monitoring during endoscopy, while supplemental O_2 is routinely administered by 39.3% of endoscopists[4]. In Greece, pulse oximetry is used in 96% of endoscopic procedures[5]. Major endoscopy societies, including those of Canada and the United States, recommend the use of pulse oximetry, continuous electrocardiogram and blood pressure, and heart rate monitoring in patients receiving propofol[11,12]. In Switzerland, pulse oximetry monitoring is currently used in more than 95% of examinations, compared with 2.5% of examinations in 1990[9]. In Germany, all patients are routinely moni-

Table 1 Percentage of sedation use in different countries

Country	Sedation	Propofol use	Benzodia-zepines alone use	Benzodiaze-pines plus opioids use	No. of nurses present during endoscopy	Pulse oximetry use	Supplemental oxygen use
Canada	90%	12%		always	1		
Italy		42.30% for ERCP (by anaesthesiologists)	50.80%	39.50%		100%	By 39.3% of endoscopists
Greece	EGD: 64%; Colonoscopy: 78%; ERCP: 100%; EUS: 100%	33.80% (in selected cases and only by anaesthesiologists)	35.30%	62.10%		96%	
United States	98%	25.70%		74.30%		98.60%	By 72.7% of endoscopists (in all EGDs)
Switzerland	78%	43% (regular use with or without the help of an anaesthesiologist)	Midazolam for the majority of endoscopies		1	95%	
Spain	EGD: 20%; Colonoscopy: 20%; ERCP: 100%; EGD: 74%	Only by anaesthesiologists	Only for EFD	Only for colonoscopies	1	77%	
Germany	Colonoscopy: 87%	74%	82%	35%		97%	34%

ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophagogastroduodenoscopy; EUS: Endoscopic ultrasound; EFD: Energy flux density.

tored by pulse oximetry, while automated blood pressure monitoring and/or electrocardiography are applied in 29 and 13% of cases, respectively. Supplemental oxygen is routinely administered to 34% of patients[7].

Data concerning endoscopy practices in developing nations are scarce. In a study comparing endoscopy practices between endoscopists practising in 46 developed and developing countries, no significant differences in the use of a benzodiazepine and opioid combination, propofol alone, or unsedated endoscopy were found. Sedation is used for most endoscopic procedures, leading to the conclusion that sedation practices do not significantly differ between developing and developed countries[13].

Table 1 provides a summary of sedation practices in some parts of the world.

DRUGS CURRENTLY USED FOR SEDATION IN GI ENDOSCOPY

Various types of sedation and analgesia techniques are used during GI endoscopy procedures. Currently, there is no standard sedation regimen, and even within individual institutions, the choice of sedation may depend on endoscopist preference and the procedure being performed. Benzodiazepines, such as alprazolam, bromazepam, brotizolam, clotiazepam, diazepam, etizolam, flunitrazepam, lorazepam, midazolam, oxazepam and triazolam, are among the most frequently prescribed drugs. These drugs act as anxiolytics, sedatives, hypnotics, amnesics, antiepileptics and muscle relaxants. Among them, midazolam is an important drug and is widely used in everyday endoscopy work. It is now considered to be the benzodiazepine of choice, as it has a shorter duration of action and a better pharmacokinetic profile than diazepam. Other drugs used for sedation include opioids (pethidine and fentanyl), propofol, ketamine and droperidol. Adequate knowledge of the pharmacokinetic properties of these agents is crucial when commencing sedation (Table 2)[14].

The special characteristics of the currently available drugs for digestive endoscopy, as well as the drugs under investigation, are shown in Table 3 and are subsequently summarised in the following sections.

Midazolam

Midazolam is most likely the most widely used drug for sedation in everyday endoscopic work. The action of midazolam is due to the potentiation of the neural inhibition mediated by gamma-aminobutyric acid. In addition to its action on the central nervous system, midazolam exhibits a dose-dependent ventilatory depressant effect and causes a reduction in arterial blood pressure and an increase in heart rate. Midazolam is metabolised by cytochrome P450 enzymes and glucuronide conjugation. CYP3A4 is important in the biotransformation of midazolam.

The duration of action of midazolam is dependent on the duration of its administration. It also has synergistic interactions with other hypnotics and opioids. Various factors, including age, compromised renal function, and liver dysfunction, affect the pharmacokinetics of the drug[15].

Clinical studies: A large number of prospective, randomised, placebo-controlled and non-controlled trials have been published in recent years concerning the efficacy and safety of midazolam alone or in combination with analgesics. The most recent of these trials are mentioned below.

In a study conducted to evaluate the prevalence of hypoxia related to midazolam sedation during upper GI endoscopy, 180 patients referred for selective endoscopy were randomised to either midazolam sedation or pla-

Table 2 Characteristics of the pharmacological agents used to achieve a moderate level of sedation in gastrointestinal endoscopy (*i.v.* administration)[1]

Agent	Chemical structure	Molecular weight (g/moL)	Onset of action (min)	Duration of action	Elimination half-life	Metabolism/excretion
Midazolam	$C_{18}H_{13}ClFN_3$	325.78	1.0-2.5	2-6 h	1.8-6.4 h	Hepatic and intestinal; excreted in urine
Propofol	$C_{12}H_{18}O$	178.27	< 1	3-10 min	Triphasic: 2.2 min, 20 min, 8 h	Hepatic; excreted in urine
Fentanyl	$C_{22}H_{28}N_2O$	336.471	⩽ 1.5	1-2 h	2-7 h	Hepatic; excreted in urine
Meperidine	$C_{15}H_{21}NO_2$	247.33	5	2-4 h	2-7 h	Hepatic; excreted in urine

[1]Modified from Manolaraki *et al*[14].

Table 3 Currently used drugs for sedation and drugs under investigation

Drugs currently used for sedation	Drugs and other practices under investigation
Midazolam	Nitrous oxide gas (N_2O)
Fentanyl	Remimazolam
Propofol	Fospropofol
	Dexmedetomidine
	Alfentanyl
	Remifentanil
	Music

cebo. The results revealed that no patients developed any serious episodes of hypoxia and that the incidence of mild hypoxia was not significantly different between the two groups. There was no significant difference in arterial oxygen saturation as recorded by the endoscopist staff[16].

In another study, haemodynamic responses during gastroscopy in healthy subjects were studied in two groups: midazolam alone *vs* midazolam in combination with meperidine. It was found that blood pressure and oxygen saturation significantly decreased with sedation in both groups during endoscopy, but no significant differences were found between the two groups. Heart rate increased significantly, whereas systolic arterial pressure, diastolic arterial pressure and O_2 saturation (SpO_2) decreased significantly, with both regimes. Patient compliance was significantly better with combined sedation[17].

Midazolam has been tested in combination with a variety of other drugs. In one study, the efficacy and safety of midazolam in combination were tested in 74 patients. The midazolam group received only midazolam, and the midazolam/meperidine group received midazolam plus meperidine. The results showed that there was no significant difference between the two groups with regard to the recovery time, procedure time and mean visual analogue scale scores[18].

In a randomised trial comparing the efficacy and recovery time of two sedation regimens consisting of midazolam in combination with either meperidine or fentanyl in patients submitted for colonoscopy, it was found that the use of fentanyl in combination with low-dose midazolam resulted in a significantly faster recovery from sedation compared with meperidine, without any apparent loss of analgesic effect[19].

The synergistic sedation with low-dose midazolam plus propofol *vs* the standard regimen of midazolam and pethidine for conscious sedation in colonoscopy was investigated in a group of patients that included a large number of elderly patients with comorbidities. The synergistic sedation with low-dose midazolam plus propofol was superior to a standard combination of midazolam and the opioid pethidine for colonoscopy in terms of patient comfort and recovery time[20].

In a prospective, randomised study, the standard regime of midazolam and pethidine *vs* a propofol-fentanyl mixture was tested. It was found that patient-controlled sedation/analgesia with propofol and fentanyl was a safe and effective combination, resulting in a high level of satisfaction for both the patient undergoing upper GI tract endoscopic ultrasonography and the endoscopist[21].

Barriga *et al*[22] evaluated the adequacy of conscious sedation during upper endoscopy using midazolam alone compared with midazolam plus fentanyl. Although, from the endoscopist's perspective, patients in the combination group had better tolerance, no significant differences were found in the patient assessments. These results suggest that an adequate level of sedation can be obtained safely by either midazolam or midazolam plus fentanyl.

Midazolam was also tested as an orally administered premedication in patients undergoing upper GI endoscopy. In a double-blind, placebo-controlled, randomised trial, 130 patients were randomised to receive either 7.5 mg of midazolam orally or a placebo as the premedication. The results showed that the median anxiety score during the procedure in the midazolam group was significantly lower than that in the control group. Moreover, a significantly greater number of patients in the midazolam group graded overall tolerance as "excellent or good" and reported partial or complete amnesia in greater degree compared with the control group. Finally, patients in the midazolam group were more willing to repeat the procedure if necessary. However, the median recovery time was significantly longer in the midazolam group than in the control group. No significant differences in the satisfaction score and haemodynamic changes between the two groups were observed[23].

In conclusion, midazolam must be considered as an excellent drug for achieving safe and effective sedation during upper and lower GI endoscopy, whether used alone or in combination with analgesics.

Propofol

The sedative-hypnotic drug propofol (2,6-diisopropylphenol) is a phenolic derivative with satisfactory sedative,

hypnotic, antiemetic and amnesic properties. Additionally, propofol the advantage of a rapid onset of action and a short recovery profile. The depth of sedation increases in a dose-dependent manner. Propofol is highly lipophilic and, therefore, can rapidly cross the blood-brain barrier, resulting in an early onset of action. Consequently, emergence from sedation is also quite rapid because of its fast redistribution into peripheral tissues. Sedation with propofol can be achieved both by bolus administration and continuous infusion. The drug can cause unconsciousness within 30 s. As an additional advantage, regardless of the length of the sedation period, recovery from propofol will occur within 10-20 min after discontinuation. Propofol also has an excellent amnesic effect and short half-life (4 min *vs* 30 min for midazolam). Currently, there is no dispute regarding propofol's superiority over benzodiazepines (with or without opioids) in terms of the abovementioned physiological effects. However, it must be strongly emphasised that titrating propofol to achieve conscious sedation without inducing general anaesthesia requires significant clinical expertise.

This drug is being increasingly used for sedation during painful diagnostic and therapeutic procedures because it increases the quality of upper GI endoscopy by increasing patients' acceptance of the procedure and improving the diagnostic accuracy of endoscopy[24].

With regard to side effects, propofol is generally associated with good haemodynamic stability, although it can induce a dose-dependent decrease in blood pressure and heart rate. Transient decreases in blood pressure are more prominent during bolus administration. Thus, slow initial infusions are recommended in most patients. Moreover, strict aseptic technique must be used during the handling of the product to prevent accidental extrinsic microbial contamination. There are also some other disadvantages of propofol, including the lack of a pharmacological antagonist. The combination of propofol and midazolam has synergistic effects and may have advantages over the use of propofol as a single agent[20]. Thus, a combined sedation regimen with a benzodiazepine retains the possibility for partial pharmacological reversibility using flumazenil.

However, data from a recent meta-analysis suggest that propofol sedation is not associated with an increased risk of complications. In fact, propofol sedation for colonoscopy was associated with lower complication rates than sedation with traditional agents[25]. Several prospective studies confirmed that lower doses were needed for combined sedation with midazolam/propofol compared with propofol alone during diagnostic or therapeutic endoscopy[26,27].

A large number of clinical trials and meta-analyses of these trials have been published, the main results of which are discussed below.

Clinical studies of propofol in upper GI tract endoscopy: A number of studies revealed that propofol offers significant advantages over benzodiazepines and opioids for sedation during endoscopic procedures. Other prospective studies indicated that propofol was safer and more effective than midazolam and meperidine for reaching and maintaining an adequate level of sedation during endoscopy, resulting in better titration of the level of sedation and a shorter recovery time[28].

A prospective study evaluated the safety and efficacy of nurse-administered, low-dose propofol sedation in 8431 adults submitted to upper GI endoscopy. Propofol was administered by bolus injection at a dose of 40 mg for patients < 70 years old, 30 mg for patients 70-89 years old, and 20 mg for patients 90 years old or older. Only 0.26% of the patients required a transient supplemental oxygen supply, and full recovery occurred in 99.9% of patients 60 min after the procedure. However, men and younger patients required significantly higher doses of propofol than women and older patients. A total of 99% of patients were willing to repeat the same procedure. This study showed that the use of only a low dose of nurse-administered propofol sedation is safe and effective for diagnostic esophagogastro-duodenoscopy[29].

Levitzky *et al*[30] showed that balanced propofol sedation targeted to induce moderate sedation in patients undergoing upper GI endoscopy results in better patient satisfaction and a shorter recovery time than standard sedation alone.

Propofol in lower GI tract endoscopy: The optimal regimen of propofol for colonoscopy sedation is still controversial. Both propofol alone and propofol in combination with opiates (meperidine) or benzodiazepines (midazolam) are frequently used during colonoscopy to achieve moderate levels of sedation. Hsieh *et al*[31] noticed that for sedated colonoscopy, propofol in combination with meperidine is better than propofol alone for improving patients' tolerance and recovery.

The combination of 1.0-2.0 mg of midazolam with either 50-100 mg of fentanyl or *i.v.* propofol of 0.5-2.5 mg/kg allowed patients to undergo colonoscopy under comparable sedative and analgesic conditions. The combination with fentanyl had a significantly smaller effect on pulse rate and blood pressure, while the combination with propofol produced more favourable results, especially in terms of superior amnestic effects[32].

In a study of 300 adults undergoing colonoscopy, the use of fentanyl in combination with low-dose midazolam was found to result in a faster recovery from sedation compared with meperidine without decreasing the analgesic effect[19].

Recently, patient-controlled sedation with propofol has been advocated as a method for dealing with the narrow therapeutic window for moderate sedation. In a relevant study, 50 patients undergoing elective colonoscopy were randomised to receive midazolam/fentanyl or propofol/remifentanil administered *via* patient-controlled sedation. Patients in the propofol/remifentanil group were sedated and recovered significantly more rapidly than patients in the midazolam/fentanyl group[33].

Propofor in therapeutic GI endoscopic procedures: In a prospective, randomised, single-blinded study of 222 patients, Lee *et al*[34] compared the safety and efficacy of balanced propofol sedation with conventional sedation (midazolam and meperidine) in patients undergoing therapeutic endoscopic procedures. They found no significant differences between the balanced propofol sedation and conventional groups with regard to the rates of cardiopulmonary complications and transient interruption of procedures, although balanced propofol sedation provided a significantly higher level of endoscopist satisfaction and better patient cooperation.

Meta-analyses of the use of propofol for sedation: To date, two meta-analyses have been published concerning the safety and efficacy of propofol for GI endoscopy.

The first meta-analysis, published in 2005, included 12 original studies with 1161 patients. Of these patients, 634 received propofol and 527 received midazolam, meperidine, and/or fentanyl. Most of the studies were randomised trials of moderate quality. It was found that the pooled odds ratio for developing hypoxia or hypotension for all of the procedures combined was 0.74 in patients using propofol. The pooled odds ratios were 0.85 for upper GI endoscopy, 0.4 for colonoscopy, and 1.07 for ERCP/EUS. Compared with traditional agents, it was noted that sedation with propofol during colonoscopy appears to result in a lower incidence of cardiopulmonary complications, although the risk of complications associated with upper GI endoscopy seems to be similar[25].

The second meta-analysis included 20 studies on the use of propofol for colonoscopy[35]. The analysis showed that recovery and discharge times were shorter with the use of propofol. There was also higher patient satisfaction with the use of propofol, although no significant differences in the procedure time, cecal intubation rate and number of complications were noticed. Finally, no difference in pain control with non-patient-controlled sedation with propofol compared with the traditional agents was noted. The only disadvantage was that pain control with propofol was inferior compared with the use of traditional agents. The general conclusion from these meta-analyses is that propofol for sedation during colonoscopy results in a faster recovery and discharge time, as well as increased patient satisfaction and acceptance rates of side effects.

In conclusion, propofol provides a faster onset of action and deeper sedation compared with standard doses of benzodiazepines and narcotics. More rapid cognitive and functional recovery should be expected when propofol is used as a single agent compared with benzodiazepines. The drug appears to have more advantages when used for prolonged and therapeutic endoscopic procedures, including ERCP and EUS. Although it can be safely and effectively used by a physician-supervised nurse, patients must be under continuous care, consistent with the care required for patients undergoing deep sedation. Personnel in the endoscopy room should be able to rescue the patient from severe respiratory depression.

Fentanyl

Fentanyl, a μ-opioid receptor agonist, is a synthetic narcotic analgesic characterised by a rapid onset and short duration of action. The action of the drug is related to its agonism of the opioid receptors. It is 100 times more potent than morphine, with 100 μg equivalent to 10 mg of morphine and 75 mg of meperidine (pethidine) in terms of analgesic activity. Its strong potency is largely due to its high lipophilicity, which also explains the rapid penetration of the drug into the central nervous system. Fentanyl binds μ-opioid G-protein-coupled receptors, which inhibits the release of pain neurotransmitters by decreasing intracellular Ca^{2+} levels. It has been used in combination with midazolam, mainly in patients undergoing lower GI endoscopy.

In a trial comparing meperidine with fentanyl, the authors noted that the total procedure time was shorter for those receiving fentanyl than for those receiving meperidine. Based on post-procedure pain scores, examinations performed using meperidine were less painful compared with those performed with fentanyl[36].

A meta-analysis compared the efficacy, safety, and efficiency of agents used for moderate sedation in upper GI endoscopy or colonoscopy in 36 studies involving a total of 3918 patients. Sedation improved patient satisfaction and the willingness of patients to repeat upper GI endoscopy compared with these measures in patients who received no sedation. Midazolam provided superior patient satisfaction and resulted in a less frequent memory of the upper GI endoscopy procedure compared with diazepam. Adverse events and patient/physician assessments were not different between midazolam (with or without narcotics) and propofol. The procedure time was similar, but sedation and recovery times were shorter with propofol than midazolam-based regimens. The results confirmed that moderate sedation provides a higher level of physician and patient satisfaction and a lower risk of serious adverse events compared with other currently available agents. Midazolam-based regimens have longer sedation and recovery times than propofol[37].

DRUGS UNDER INVESTIGATION FOR GI ENDOSCOPY

Various other drugs are also under investigation for GI endoscopy. Among them, prodrug formulations of propofol have been developed to overcome the disadvantages of the lipid-based formulations. So far, the results of the relevant studies appear promising. The most important clinical data are presented below.

Nitrous oxide gas

Nitrous oxide gas (N_2O) (molecular mass 44.013) has been proposed as an alternative to *i.v.* analgesia in patients undergoing lower GI endoscopy. N_2O/O_2 mixtures have a satisfactory analgesic effect and short half-lives, thus providing an alternative method of sedation for colonoscopy procedures.

A systematic review of 11 randomised studies including 623 patients was published in 2010[38]. In these studies, N_2O was compared with a lack of sedation in patients undergoing either flexible sigmoidoscopy or colonoscopy. The results revealed that patient-reported pain was similar for N_2O when undergoing flexible sigmoidoscopy *vs* no sedation and when undergoing colonoscopy *vs i.v.* sedation. No differences in duration, procedure difficulty or complications were identified. N_2O was associated with a more rapid recovery than *i.v.* sedation. This systematic review supports the assumption that N_2O provides comparable analgesia to *i.v.* sedation in patients undergoing colonoscopy. Rapid recovery enables quicker patient discharge and removes the need for a patient to be chaperoned.

In a more recent Cochrane review, 257 patients were randomised to receive a N_2O/O_2 mixture (7 studies), while 225 patients received some form of sedation with or without additional analgesia (6 studies) and 65 patients received placebo (3 studies). Four studies showed that N_2O/O_2 reduced pain/discomfort compared with conventional methods, whereas one study showed that sedation was better and another study showed that N_2O/O_2 was better. Six studies showed that N_2O/O_2 groups had a quicker recovery time and shorter length of hospital stay, whereas one study showed no difference between the two groups. Two studies showed that N_2O/O_2 was safer, whereas one showed that sedation was safer. The conclusion was that N_2O is as efficient as and safer than other pain relief methods used during colonoscopy[39].

A randomised clinical trial compared the efficacy of Entonox (50% N_2O and 50% O_2) with midazolam-fentanyl sedation in 131 patients undergoing elective colonoscopy. Sixty-five patients received Entonox, and 66 patients received midazolam-fentanyl. Patients receiving Entonox had a shorter time to discharge. They also reported significantly less pain and better recovery of psychomotor function immediately after the procedure and at discharge. Patients who received Entonox also reported a higher level of satisfaction. Again, this study concluded that Entonox provides better pain relief and faster recovery than midazolam-fentanyl in patients undergoing elective colonoscopy[40].

A double-blind, randomised, placebo-controlled trial showed that N_2O inhaled intermittently is not an effective substitution for *i.v.* on-demand sedation in the setting of colonoscopy without sedation. In this study, patients inhaled N_2O or placebo on demand. The median patient-reported pain level was 2 in both the N_2O and control groups. Additional sedatives and analgesics were given equally often and at similar doses in both groups. No side effects related to the administration of N_2O were noted[41].

In conclusion, the available data suggest that N_2O is an effective analgesic and sedative agent that must be further investigated in larger studies.

Remimazolam

Remimazolam ($C_{21}H_{19}B_rN_4O_2$; molecular weight 439.304) is a short-acting GABA(A) receptor agonist that exhibits organ-independent metabolism, which was developed as an *i.v.* sedative agent for use in day-case procedures and the induction and maintenance of anaesthesia.

Preclinical studies in animals demonstrated that remimazolam caused a more rapid onset and a shorter duration of action compared with midazolam.

In a phase Ⅱ a clinical trial evaluating remimazolam as a procedural sedative for upper GI endoscopy, the time to recovery from sedation was shorter and more consistent with remimazolam compared with midazolam. Because of its organ-independent metabolism and rapid and predictable onset and recovery profile, remimazolam appears to have potential advantages over other currently available short-acting benzodiazepines. However, its respiratory depressant effect has been reported in numerous studies[42].

Fospropofol

Various prodrug formulations of propofol have been developed to overcome the disadvantages of the lipid-based formulations, the complications of lipid infusion, and the risk of fluctuations in propofol plasma levels due to bolus injection.

Fospropofol ($C_{13}H_{19}Na_2O_5P$, molecular weight: 332.24) is a water-soluble prodrug of propofol, metabolised *in vivo* to produce liberated propofol (producing the sedative effect), phosphate and formaldehyde. After *i.v.* injection, propofol is released from fospropofol by tissue alkaline phosphatases with a pattern of plasma concentrations, resulting in lower peak concentrations and a more gradual decline in drug concentrations compared with standard propofol administration protocols. As a result, the drug has pharmacokinetic and pharmacodynamic properties that differ from those of propofol emulsion. The time of the peak sedative effect after a bolus injection fluctuates between 3 and 7.5 min, compared with 1 min 36 s for propofol[43]. Fospropofol was generally well tolerated in clinical trials. Adverse events are mostly of mild-to-moderate severity and are transient and self-limiting[44].

The 6.5-mg/kg dose of fospropofol provides the ideal balance of efficacy and safety for patients undergoing colonoscopy. In a double-blind trial evaluating 127 patients who received fospropofol (2, 5, 6.5 or 8 mg/kg) or midazolam 0.02 mg/kg following pre-treatment with fentanyl, fospropofol yielded a significant dose-dependent increase in sedation success from 24% (2 mg/kg), 35% (5 mg/kg) and 69% (6.5 mg/kg) to 96% (8 mg/kg; $P < 0.001$)[45].

The same group of authors evaluated the efficacy and safety of *i.v.* fospropofol administration in patients undergoing colonoscopy for moderate sedation. Patients were randomised to receive fospropofol 2 mg/kg, fospropofol 6.5 mg/kg, or midazolam 0.02 mg/kg after pretreatment with *i.v.* fentanyl 50 μg. The results showed that sedation success was higher in the fospropofol 6.5 mg/kg group compared with the 2 mg/kg group (87% *vs* 26%; $P < 0.001$) and was 69% in the midazolam group.

Most adverse events were mild to moderate in intensity, the most common being paraesthesias (68% *vs* 60%) and pruritus (16% *vs* 26%) in the fospropofol 6.5 and 2 mg/kg groups, respectively. Fospropofol 6.5 mg/kg was associated with higher rates of sedation success, memory retention, and physician satisfaction than fospropofol 2 mg/kg[46].

Together, these results suggest that fospropofol is a promising drug requiring further investigation.

Dexmedetomidine

Dexmedetomidine ($C_{13}H_{16}N_2$, molecular mass: 200.28), a pharmacologically active dextroisomer of medetomidine, is a selective α(2)-adrenergic receptor agonist. It is indicated for the sedation of mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures[47]. The drug should be administered *i.v.* only by experienced individuals, and the patient must be continuously monitored. Additionally, the dose must be adjusted in patients with liver and renal failure, as well as in elderly patients.

Dexmedetomidine can be safely used as a sedoanalgesic agent in colonoscopies because it provides efficient haemodynamic stability, higher satisfaction scores and lower Numeric Rating Scale scores. A study comparing dexmedetomidine (1 μg/kg and as a continuous infusion dose of 0.5 μg/kg per hour) with midazolam (0.05 mg/kg) plus fentanyl citrate (1 μg/kg) with regard to perioperative haemodynamics, sedation, pain, satisfaction and recovery scores during colonoscopy showed that, although statistically significant differences in mean arterial pressure were not detected between the two groups, heart rates were higher and SpO_2 scores were lower in dexmedetomidine group. When the groups were compared using the Ramsay sedation scale, the scores of group I at the 10th and 15th minute were significantly lower than those of group II[48].

In a recent study, Takimoto *et al*[49] showed that sedation with dexmedetomidine is a safe and effective practice in patients with gastric tumours undergoing endoscopic mucosal resection. In their study, 90 patients with gastric tumours were sedated with either dexmedetomidine [*i.v.* infusion of 3.0 μg/kg per hour over 5 min, followed by continuous infusion at 0.4 μg/kg per hour (n = 30), propofol (n = 30), or midazolam (n = 30)]. In all groups, 1 mg of dexmedetomidine was added *i.v.* as needed. The results showed that none of the dexmedetomidine-sedated patients exhibited a significant reduction in oxygen saturation level. Fewer patients in the dexmedetomidine group showed body movement during endoscopy compared with the other groups. The rate of effective sedation was significantly higher in the dexmedetomidine group compared with the midazolam and propofol groups. The mean duration of endoscopic submucosal dissection in the dexmedetomidine group was significantly shorter than that in the other two groups. However, dexmedetomidine alone is most likely not as effective as propofol combined with fentanyl for providing conscious sedation during ERCP, exhibiting concurrently greater haemodynamic instability and prolonged recovery[50].

Alfentanyl

Alfentanyl ($C_{21}H_{32}N_6O_3$, molecular weight: 452.98) is a narcotic analgesic with a rapid onset of action, a very short duration of action, and a potency of approximately one-third that of fentanyl. Recently, it was shown that patient-controlled analgesia pumps and sedation with alfentanyl and fentanyl for colonoscopy are safe, feasible, and acceptable to most patients, although a shorter sedation time makes alfentanyl more attractive, as it reduces the postprocedural workload[51].

Remifentanil

Remifentanil ($C_{20}H_{28}N_2O_5$, molecular weight: 376.447) is a μ-opioid receptor agonist that has important neuroanaesthesia characteristics. It has been used in a small number of clinical trials in patients undergoing GI endoscopic procedures. There are many reports of the use of remifentanil in different settings, including GI endoscopy, with or without background infusion, and the quality of analgesia and patient satisfaction seem to be the same as with standard sedation/analgesia. It seems that remifentanil patient-controlled analgesia is safe and effective for inducing sedoanalgesia during colonoscopy.

In a randomised, double-blind clinical trial, 60 patients undergoing colonoscopy were randomly assigned to either the remifentanil or meperidine group. All of the patients received premedication with midazolam 0.03 mg/kg *i.v.* In the remifentanil group, a bolus dose of remifentanil was given, and a patient-controlled sedation/analgesia pump was set to inject further bolus doses, while patients in the meperidine group received a bolus of meperidine and a sham, patient-controlled sedation analgesia pump. The degree of pain, level of satisfaction with sedoanalgesia of patients and gastroenterologists, and degree of difficulty experienced by the endoscopist, as well as the discharge time and duration of colonoscopy, were not different between the two groups[52].

In another study, the safety and efficacy of remifentanil during colonoscopy compared with the standard combination of midazolam and pethidine were tested in 116 patients who received either midazolam and pethidine or remifentanil only. Recovery was found to be faster in the remifentanil group. There was also a significant difference with regard to the time of hospital discharge. In this study, remifentanil during colonoscopy provided sufficient pain relief with better haemodynamic stability, less respiratory depression, and significantly faster recovery and hospital discharge times than moderate sedation with midazolam and pethidine[53]. However, further studies are needed to confirm these interesting results.

Music

Among methods reported to minimise patient discomfort during GI endoscopy (especially colonoscopy), mu-

sic has been utilised as an important therapeutic tool for effectively relieving stress and inducing analgesia. During recent years, several papers investigating the efficacy of music on patients' stress and pain relief were published. The most important of these publications are discussed below.

Clinical trials concerning the role of music in sedation: More recent clinical trials not included in the abovementioned meta-analyses have revealed rather conflicting results.

In a single-blind, randomised, controlled trial, the authors showed that music significantly reduces discomfort and, consequently, should be routinely provided to patients undergoing colonoscopy. In this study, 109 patients were randomised to receive music-delivering or non-sound-emitting headphones before and during endoscopy. The results revealed that the mean pain score was significantly lower in the music group compared with the control group, while overall satisfaction and willingness to repeat the procedure were significantly improved and the difficulty perceived by physicians was significantly reduced. Interestingly, the total amount of midazolam and pethidine was significantly lower in the music group compared with the control group[54].

Music in the endoscopy room was also found to reduce the anxiety levels in patients undergoing endoscopic procedures. In a controlled trial of 180 patients, the effect of age and type of endoscopic procedure on anxiety levels upon arrival in the unit and immediately before the endoscopy procedure after listening to music or no music (control group) for the same period was investigated. Although anxiety levels were not influenced by age or procedure, it was found that listening to music resulted in a significant reduction in anxiety scores, which was maintained for all age groups, irrespective of the type of endoscopic procedure performed. The authors suggest that providing music in the endoscopy unit is a simple strategy that can improve the well-being of patients[55].

Another study, which was specifically designed to investigate whether listening to music reduced the pain experienced by patients during sigmoidoscopy without sedation or analgesia, concluded that listening to music did not reduce pain intensity. In this study, it was found that the mean pain intensity in the music group was not different from that in the control group, and the proportion of patients with at least moderate pain during sigmoidoscopy did not differ between the two groups[56].

Meta-analyses concerning the role of music in sedation: Three meta-analyses regarding the role of music in sedation have been published to date. At least two of them suggested that music can effectively relieve stress and improve the level of analgesia during GI endoscopy. In the first of these meta-analyses, the authors included six randomised, controlled trials with a total of 641 patients. They found that in studies that did not use pharmacotherapy, patients receiving music therapy exhibited significantly lower anxiety levels compared with controls. Additionally, in studies in which pharmacotherapy was used, patients receiving music therapy exhibited significant reductions in analgesia requirements and an almost significant reduction in sedation requirements compared with controls. Furthermore, the procedure time was significantly reduced in the music therapy group compared with the control group. The authors' conclusion was that music therapy is an effective tool for stress relief and analgesia in patients undergoing GI endoscopic procedures[57].

In the second meta-analysis, which was published in 2008 and focused on colonoscopy, the authors included 8 studies with a total of 722 patients. In four studies, music was transmitted through headphones/earphones (as background music in three studies, and one study did not specify the media method). The results showed that the combined mean time taken for the colonoscopy procedure was shorter in the music group compared with the control group. There was weak evidence of benefit regarding the pain score, blood pressure, and mean recovery time in the music group compared with the control group. No harmful effects from listening to music were reported in any of the studies in this meta-analysis. The only disadvantage found in allowing patients to listen to music through headphones/earphones was the isolation of patients from the medical staff during the procedure. The authors concluded that "listening to music is effective in reducing procedure time and amount of sedation during colonoscopy and should be promoted"[58].

Finally, in the third meta-analysis, which was published in 2009 and included 8 studies with a total of 712 patients, it was found that patients' overall experience scores were significantly improved when they were allowed to listen to music. However, no significant differences were noted in patients' pain scores, mean doses of midazolam and meperidine, procedure time, and willingness to repeat the same procedure in the future, indicating that music improves only patients' overall experience with colonoscopy[59].

One possible explanation for the reduction in the doses used for sedation sedation is that patients in the music group are more relaxed and have less anxiety, resulting in a faster completion of the procedure and the use of less sedation[60]. The reduction in procedure time implies a reduction in the time during which patients feel anxious, frightened, and uncomfortable while undergoing the procedure and may be useful in enhancing the compliance rate. The avoidance of sedation may obviously result in a quicker patient discharge, less need for monitoring, and overall cost savings. Two other advantages of music are its inexpensiveness and ease of implementation[61].

In conclusion, it seems that listening to music, especially during colonoscopy, could reduce the procedure time, anxiety, and amount of sedation needed, without producing any harmful events. As a result, music should be promoted because of its beneficial effect and negligi-

ble cost. However, several aspects of this method, such as the choice of music and the mode of transmission, are worth further investigation.

SEDATION FOR GI ENDOSCOPY IN SPECIAL CLINICAL SITUATIONS

A large number of situations require special attention not only at the beginning of the endoscopic procedure but also during the procedure and recovery. The drugs that must be used, along with the precautions that must be followed, are analysed below.

Obesity

Obesity is a significant health problem that has assumed epidemic proportions. As a result, the number of obese patients requiring endoscopy is increasing. Morbid obesity can result in pulmonary hypertension, obstructive sleep apnoea, and restrictive lung disease. It is relatively unknown how safe the current practices of sedation for endoscopic procedures are in bariatric patients[62]. Therefore, special consideration should be given to these patients, and endoscopists need to be aware of challenges that may be present while performing endoscopic procedures in obese patients[63].

There are limited data on the use of sedation in obese patients. Studies published to date refer mainly to the use of sedation in obese subjects undergoing advanced endoscopic procedures or upper GI endoscopy before bariatric surgery.

In a study involving 69 subjects with morbid obesity submitted to upper GI endoscopy before bariatric surgery, the authors administered sedation with propofol at a mean dose of 380 ± 150 mg (range 80-900 mg). Two patients developed severe hypoxemia, which required bronchoscopic intratracheal O_2 insufflation. Thus, although upper GI endoscopy can be performed safely in obese patients, careful monitoring and anesthesiological support are required, especially in patients with concomitant diseases[64].

In a study investigating the safety of anaesthesia-assisted endoscopy using propofol-mediated sedation in subjects undergoing advanced endoscopic procedures, the authors found that an increased body mass index was associated with an increased frequency of airway manoeuvres and hypoxemia. A multivariate analysis revealed that body mass index was an independent predictor of the appearance of sedation-related complications. Interestingly, in obese individuals, there was no difference in the frequency of sedation-related complications in patients receiving propofol alone or in combination with other drugs. Propofol sedation can be safely used in obese patients undergoing advanced endoscopic procedures when administered by trained professionals, despite the increased frequency of sedation-related complications[65].

Finally, it was found that patients who undergo upper GI endoscopy with either anaesthesiologist- or surgeon-monitored sedation seem to tolerate the procedure equally well. However, significantly fewer patients in the anaesthesiologist-monitored sedation group complained of throat pain after the procedure and/or remembered gagging during the procedure, thus leading to the conclusion that anaesthesiologist-monitored sedation should be considered in patients undergoing preoperative upper endoscopy before bariatric surgery[66].

In conclusion, although quite safe, moderate sedation during endoscopy may pose some risks to obese patients. In particular, the presence of obstructive sleep apnoea may identify a subset of patients at higher risk of complications. Further studies are required in this field, as the number of subjects undergoing bariatric surgery is constantly increasing worldwide.

Chronic liver disease

Endoscopy, either diagnostic and/or therapeutic, is often necessary in patients with chronic liver disease, sometimes on an emergency basis. It is well established that liver disease may impair the metabolism of drugs usually administered for sedation. The evaluation of patients with chronic liver disease before endoscopy should include a full assessment of hepatic function, as well as a complete physical examination to exclude the possibility of the presence of hepatic encephalopathy. As a general rule, sedation should be used especially in patients undergoing ligation of acutely bleeding varices, although in some cases sedation is not necessary[67].

Liver dysfunction could reduce both the clearance of the drugs eliminated by hepatic metabolism or biliary excretion and plasma protein binding. Chronic liver disease is also associated with a reduction in drug-metabolising activities, such as the activity of the CYP450 enzymes. In patients with advanced cirrhosis, it is necessary to adjust the dose of those drugs eliminated by renal excretion[68].

Concerning the drugs used in the sedation of cirrhotic patients, most authors prefer to use propofol instead of benzodiazepines and opioids because of its short biological half-life and lower risk of provoking hepatic encephalopathy.

In a recently performed study, the authors compared sedation with combinations of propofol plus fentanyl and midazolam plus fentanyl in 210 cirrhotic patients undergoing upper GI endoscopy. The doses of midazolam and propofol were 0.05 and 0.25 mg/kg, respectively, while the dose of fentanyl was 50 μg *i.v.* in both groups. It was found that sedation with propofol was more effective and yielded a shorter recovery time than sedation with midazolam, indicating that it is a safe and effective regimen[69].

Another study reported that the use of propofol in patients with cirrhosis does not precipitate minimal or overt hepatic encephalopathy during upper GI endoscopy[70]. The results of this study were recently confirmed in a study showing that sedation with propofol in patients with compensated liver cirrhosis resulted in a shorter time to both recovery and discharge than midazolam, thus not exacerbating sub-clinical hepatic encephalopathy[71].

These results are in accordance with those described in a previous study that demonstrated that propofol sedation does not cause deterioration of minimal hepatic encephalopathy concurrently associated with improved recovery in patients with liver cirrhosis[72].

In conclusion, propofol represents a safe and effective sedation drug that could be used as an alternative to midazolam in patients with liver cirrhosis[73].

Pregnancy

Despite the fact that endoscopy is rarely required during pregnancy and is generally considered to be safe, endoscopists must be aware of the potential risks concerning both the mother and the foetus. Before endoscopy, the endoscopist must calculate the potential foetal risks, mainly due to sedation, and try to correct any possible maternal pathological situation, including hypoxia and hypotension.

During endoscopy, pregnant women should be carefully monitored by continuous electrocardiography, pulse oximetry, and intermittent blood pressure estimation[74].

Sedative drugs comprise a significant foetal risk during endoscopy in pregnant women because of the risk of hypoxia. Additionally, the exposure of pregnant women to radiation during ERCP represents another important risk that should be reduced as much as possible.

Currently, there is no evidence that endoscopy precipitates premature labour. If possible, endoscopic procedures must be performed without any sedation or, alternatively, by administering the lowest effective dose of sedative medication.

Regarding the types of drugs used for sedation, the available literature suggests that midazolam appears to be safe if used carefully[75].

ERCP is rarely necessary during pregnancy, although it cannot be avoided in pregnant women with recurrent biliary colic, abnormal liver function tests, and a dilated bile duct. A relevant study showed that ERCP can be safely performed during pregnancy, leading to successful treatment in almost all patients. Sedation is uneventful for all pregnant women and their foetuses. However, it must be recognised that pregnancy may be associated with a higher rate of post-ERCP pancreatitis compared with the general population[76]. The same conclusion was reached in another study, the authors of which noted that ERCP is a safe procedure during pregnancy, even if the placement of a biliary stent is necessary[77].

In conclusion, upper GI endoscopy, including therapeutic interventions such as the banding of oesophageal varices, seems to be relatively safe for the foetus, although it should be performed only when strongly indicated. Similarly, flexible sigmoidoscopy also appears to be safe for the foetus and, again, should only be performed when strongly indicated. Colonoscopy data suggest that this procedure should be performed only during the second trimester and only if there is a strong indication. Finally, ERCP seems to be relatively safe but should only be performed if there is a strong indication for its use. Sedation is rather safe in ERCP, and midazolam is the preferred pharmaceutical agent by most endoscopists. As a general rule, it may be suggested that endoscopy in pregnant women should always be performed in a hospital by an expert endoscopist and only when strongly indicated[78].

Sedation in celiac disease

It has been suggested that patients with celiac disease exhibit increased rates of neuropsychiatric disturbances and visceral hypersensitivity. In a retrospective cohort study, Lebwohl *et al*[79] noted that 26% of patients with celiac disease required higher amounts of both opioids and midazolam compared with age- and gender-matched controls, possibly due to increased visceral hypersensitivity, chronic opioid/anxiolytic use, and/or underlying neuropsychiatric illness.

Sedation in the elderly

Although GI endoscopy with sedation is increasingly performed in elderly patients, data on the outcomes and side effects of sedation are limited. Age-related pharmacokinetic changes and the presence of comorbidities and polypharmacy complicate drug therapy. Aging results in impairment in the function of multiple organs, including the liver, which may also affect drug metabolism and pharmacokinetics. In addition, older people often have to consume a variety of drugs, the bioavailability of which could be increased. Additionally, lipophilic drugs may have a prolonged half-life. Combined with reduced hepatic and renal clearance mechanisms, this prolonged half-life can prolong the recovery of elderly patients after sedation. In the elderly, hepatic drug clearance of some drugs can be reduced by up to 30%. Midazolam is indicated because there are no major differences in CYP3A4 activity between young and old people. Finally, renal excretion is decreased in most elderly individuals because of the presence of hypertension and coronary heart disease[80].

In the geriatric population, conscious sedation practices are modified by the administration of fewer agents at a slower rate and lower cumulative dose. Midazolam has been widely used in elderly patients[81]. Under certain circumstances, it seems that the benefits, in terms of tolerance of low-dose midazolam for upper GI endoscopic sedation, outweigh the risks in older people. Christe *et al*[82], in a randomised, double-blind, placebo-controlled study, administered either midazolam (30 μg/kg *i.v.*) or saline (placebo) to 65 geriatric inpatients undergoing upper GI endoscopy. The results revealed that midazolam increased the probability of good tolerance. Midazolam resulted in a 10-mmHg reduction in the mean arterial pressure without inducing clinically significant hypotension. Finally, midazolam was associated with a higher risk of hypoxemia after endoscopy, but not of confusion.

In a recent study, it was found that elderly patients submitted for endoscopy required lower mean propofol doses for sedation compared with patients aged < 70

years. No major complications and no difference in the number of minor complications were noted. A favourable safety profile for combined sedation with midazolam/propofol and a higher sensitivity to propofol must be expected in patients older than 70 years of age who have various co-morbidities[83].

A study evaluating the safety of sedation with propofol in patients > 90 years of age showed that for upper GI endoscopy, percutaneous endoscopic gastrostomy, colonoscopy, and ERCP, the mean propofol doses used were 22, 24, 46 and 42 mg, respectively. In upper GI endoscopy, the level of sedation and propofol blood concentrations after administration of the drug in the group of patients > 90 years of age corresponded to those resulting from propofol use in middle-aged patients[84].

Finally, Martínez *et al*[85] found that continuous propofol sedation in patients > 80 years of age is generally as safe as in younger patients, although patients > 80 years showed a greater tendency to develop severe oxygen desaturation during the colonoscopy and endoscopic ultrasonography procedures. In general, there were no significant differences in sedation-related complications between the two groups.

Sedation in time-consuming endoscopic procedures

Time-consuming endoscopic procedures, such as ERCP, endoscopic ultrasonography and endoscopic mucosal resection, require sedation for a significantly longer period of time compared with routine upper and lower GI tract endoscopy. Moreover, endoscopic submucosal dissection for early gastric cancer generally lasts much longer than conventional endoscopy and usually requires moderate-to-deep sedation with close surveillance to ensure patient safety, thus increasing the risks related to sedation and analgesia. Therefore, the administration of safe sedation of a satisfactory degree for a longer period of time is necessary.

During recent years, a significant number of papers have been published examining the most suitable and effective drug or combination of drugs for these complex procedures. The data from these clinical studies are discussed below.

Concerning ERCP, a study comparing satisfaction, recovery scores, and safety profiles for ERCP sedation between continuous infusion of propofol and conventional sedation revealed that the continuous infusion of propofol for ERCP under the direction of a gastroenterologist yields no differences in the procedure completion rate and adverse profiles compared with intermittent meperidine and midazolam injection. However, the infusion of propofol does provide a better recovery profile[86].

It is well known that the dose requirements and complications of propofol are less when used in the diluted form than when used in the undiluted form. In a study investigating diluted and undiluted propofol requirements and recovery time in patients undergoing ERCP, it was shown that the requirements in both groups were comparable, although the incidence of sedation-related hypotension was lower in the diluted group[87].

An interesting study showed that patient-controlled sedation with propofol/remifentanil seems to be a well-accepted sedation regimen for ERCP. Additionally, the study showed that anaesthesiologist-managed propofol sedation using constant propofol infusion is associated with deep sedation without any impact on the degree of patient or gastroenterologist satisfaction[88].

EUS and ERCP can be safely performed under conscious sedation on the same day with minimal adverse events. However, combined procedures are associated with higher doses of sedatives and a slightly longer recovery time[89].

Finally, another interesting study suggested that synergistic sedation with an oral dose (7.5 mg) of midazolam 30 min before *i.v.* propofol is given combined with *i.v.* propofol could result in a significant reduction in the dosage of propofol required and in patient anxiety levels before ERCP[27].

With regard to endoscopic ultrasonography, a prospective, randomised study demonstrated that patient-controlled sedation/analgesia with propofol and fentanyl is a more effective and safe technique compared with midazolam and pethidine, resulting in a high level of satisfaction of both patients and endoscopists[21].

Concerning endoscopic mucosal dissection (ESD) for early gastric cancer, a recent study in Japan revealed that ESD performed under sedation using continuous propofol infusion for early gastric cancer was as safe as ESD performed using intermittent midazolam injection. Moreover, patients treated with continuous propofol administration experienced a quicker recovery time than those treated with midazolam[90].

A more recent study, also from Japan, confirmed the results of the study by Kiriyama *et al*[90] and suggested that propofol is as safe and effective as midazolam during ESD. Despite these promising results, sedation guidelines for the use of propofol in early gastric cancer are needed[91].

Among the newer drugs used for sedation and analgesia during GI endoscopy, dexmedetomidine has been used in patients with early gastric cancer undergoing ESD. In a randomised study of 90 patients who underwent ESD treatment, sedation was achieved with either dexmedetomidine (3.0 μg/kg *i.v.* per hour over 5 min, followed by continuous infusion at 0.4 μg/kg per hour), propofol, or midazolam. It was shown that none of the dexmedetomidine-sedated patients developed a significant reduction in the oxygen saturation level. The rate of effective sedation was significantly higher in the dexmedetomidine group compared with the other two groups. It seems, therefore, that sedation with dexmedetomidine is safe and effective in patients with gastric tumours who are undergoing ESD[49].

ADVERSE EVENTS DURING SEDATION FOR ENDOSCOPY

Sedation is usually safe; however, complications may occur, although in various proportions depending on a

number of factors, including the type, dose and mode of administration of sedative drugs, as well as the patient's age and underlying chronic disorders. A large number of side effects, including hypotension, desaturation, bradycardia, hypertension, arrhythmia, aspiration, respiratory depression, vomiting, cardiac arrest, respiratory arrest, angina, hypoglycaemia, and/or allergic reaction, have been reported.

A study in patients submitted to colonoscopic examination showed that midazolam combined with propofol appeared to influence the pulse rate and blood pressure at a significantly higher rate than a combination with fentanyl or midazolam alone. The combination with fentanyl had a significantly lower effect on pulse rate and blood pressure[32].

Prolonged hypoxemia (oxygen saturation of < 90% for ⩾ 15 s) and apnoea (lack of respiratory activity for ⩾ 15 s) are not uncommon during moderate sedation for endoscopy. In a related study, it was noted that hypoxemia usually occurs within 5 min of medication administration or endoscope intubation and that only 1/3 of all apnoea/abnormal ventilation events lead to hypoxemia. Additionally, the total dose of meperidine/fentanyl and the total dose of midazolam are predictors of apnoea[92].

Dreaming is commonly reported after propofol-based sedation. In a relevant study, the per cent of patients reporting dreaming was 19%. It seems that this phenomenon appeared more frequently in patients who received high doses of propofol and in patients who had lower bispectral index values during sedation[93].

In a study of 17 999 endoscopic procedures performed over 8 years, the authors concluded that deep sedation during endoscopic procedures is safe[94]. They noted that adverse events occurred in a small proportion of patients (4.5%) and that six complications, i.e., hypotension, desaturation, bradycardia, hypertension, arrhythmia, and aspiration, occurred in more than 0.1% of patients.

Conigliaro *et al*[95] found a percentage of 0.47% of complications related to endoscopy in patients undergoing colonoscopy when sedation was used as recommended by the guidelines.

The administration of propofol as a sedative agent in GI endoscopy resulted in a significant reduction in mean arterial pressure compared with pre-intervention values, although severe hypotension (systolic blood pressure < 60 mmHg) was noted in 0.5% of patients. Oxygen saturation decreased from 96.5% to 94.4%, although a critical decrease in oxygen saturation (< 90%) was documented in only 2.4% of patients[28].

In cirrhotic outpatients undergoing upper GI endoscopy, sedation with a combination of propofol plus fentanyl or midazolam plus fentanyl revealed no significant differences in the rate of complications between the two groups (14% *vs* 7.3%). In this study, both sedation schemes appeared to be safe[69].

Another study revealed no significant differences in complication rates between propofol deep sedation and meperidine/midazolam administered for moderate sedation. In this study, the complication rate with propofol was 0.60%, compared with 1% in the historical case-control (meperidine/midazolam moderate sedation) group[96]. Among the 324 737 unique procedures performed in patients under conscious sedation, unplanned events were reported in 1.4% of the procedures, 0.9% of which were associated with unplanned cardiopulmonary events[97]. Ljubicić *et al*[98] observed a decrease in oxygen saturation to < 85% and a temporary decrease in heart rate to < 50 beats/min in 5.5 and 11.8% of patients receiving propofol for endoscopy, respectively. Finally, Amornyotin *et al*[87] noted significantly different overall complication rates of 18.2% and 42.9%, respectively, between patients receiving diluted or undiluted propofol for ERCP. Significant differences were also noted in the overall rate of cardiovascular events.

In conclusion, sedation in GI endoscopic procedures, even in time-consuming procedures, seems to be safe. The rate of complications, either cardiovascular or respiratory, could be characterised as "acceptable", provided that all prevention measures have been adopted and the endoscopy staff is suitably equipped, properly trained in the handling of possible complications, and ready to immediately apply rescue measures. Table 4 lists the main sedation-related adverse events occurring during endoscopy in clinical trials, while Table 5 shows the main adverse effects related to the administration of drugs used for sedation in GI endoscopy.

LEGAL ISSUES RELATED TO SEDATION IN GI ENDOSCOPY

Important medical and legal issues regarding sedation have been raised during recent years. Such issues include informed consent of the patient, difficulties in assessing withdrawal of consent in a sedated patient, and the need for sedation monitoring that meets accepted standard of care guidelines[99]. Other controversies possibly related to medico-legal aspects include both the use of propofol and the administration of sedation by anaesthesia personnel. The former controversy is extremely important from a legal point of view if the continuously increasing use of propofol in GI endoscopy by non-anaesth esiologists is taken into account. In a related article, Axon emphasises the possible clinical negligence that could be associated with sedation administration. Interestingly, while the law recognises the desirability of sedation in endoscopy procedures, the facts of a particular case will be scrutinised to determine possible responsibilities of the endoscopist if an adverse outcome occurs[100]. Some questions related to the administration of sedation during GI endoscopy are discussed below.

Should sedation be administered by an endoscopist gastroenterologist or an endoscopist nurse?

The optimal drug for sedation administered by non-anaesthesiologists should have certain properties, such as a

Table 4 Main adverse events related to sedation occurring during endoscopy in clinical trials

Ref.	Drug regimen	Percentage of side effects	Severe hypotension (< 60 mmHg)	Severe desaturation (< 90%)
Ljubicić *et al*[98]	Propofol	17.3% (including bradycardia: 11.8%)		5.5%
Conigliaro *et al*[95]	Midazolam	0.47%		
Gasparović *et al*[28]	Propofol	2.9%	0.5%	2.4%
Sharma *et al*[97]	Cardiopulmonary events	EGD: 0.6%; Colonoscopy: 1.1%; ERCP: 2.1%; EUS: 0.9%		
Nayar *et al*[96]	Propofol deep sedation *vs* moderate sedation	0.6% *vs* 1.0%	0.1%	0.1% (apnoea: 0.3%)
Correia *et al*[69]	Midazolam plus propofol *vs* midazolam plus fentanyl	14% *vs* 7.3%		
Amornyotin *et al*[87]	Diluted *vs* undiluted propofol for deep sedation	18.2% *vs* 42.9%	11.4% *vs* 31.0%	0 *vs* 2.4%
Wang *et al*[32]	Midazolam *vs* midazolam combined with either fentanyl or propofol		Midazolam combined with propofol resulted in hypotension and bradycardia more significantly than a combination with fentanyl or midazolam alone	

EUS: Endoscopic Ultrasound; EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 5 Side effects related to the administration of drugs used for sedation in gastrointestinal endoscopy

Side effect	Midazolam	Propofol	Fentanyl
Hypotension	Yes	Yes	
Hypertension		Yes	
Heart rate alterations	Arrhythmia	Decrease	Arrhythmia
Respiratorydepression	Yes	Yes	Yes (particularly in the elderly)
Apnoea	Yes (in combination with fentanyl)	Yes	Yes (in combination with Midazolam)
Dystonia		Yes	Yes
Priapism		Yes	Yes (very rarely)
Pain on injection		Yes	
Lactic acidosis		Yes	
Intraocular pressure changes		Decrease	
Myoclonic movements		Yes	
Nervous system side effects	Yes (especially in the elderly)	Rare	Yes
Unusual dreams		Yes	
Hypersensitivity	Yes	Yes	Yes (rarely)
Liver damage		Yes	
Amnesia	Yes		
Impairment of cognitive functions - inability to drive safely	Yes		
Paradoxical behaviour	Yes	Yes	
Gastrointestinal effects (nausea, vomiting, hiccups, diarrhoea)	Yes	Yes	Yes
Sexual disinhibition	Yes		
Potential for abuse			Yes
Haemolysis			Yes (slow injection rates and/or mixture in isotonic fluid)

predictable pharmacokinetic profile, rapid onset of action, analgesic and anxiolytic effects, short recovery time, and minimal associated risks, thus making the presence of an anaesthesiologist unnecessary.

There is evidence suggesting that non-anaesthetists can administer sedative drugs, including propofol, safely and effectively in most cases[101].

In the last decade, a number of studies addressed the safety and efficacy of the administration of propofol during GI endoscopy by either physicians or trained nurses[102,103].

With regard to the occurrence of major side effects in these studies, there were no cases of death among patients submitted to endotracheal intubation. In a prospective trial involving 36 743 cases of nurse-administered propofol sedation, the authors concluded that adequately trained nurses and endoscopists can safely administer propofol[104].

Rex *et al*[105], in a safety review of 646 080 (223 656 published and 422 424 unpublished) endoscopist-directed propofol sedation cases, noted that endotracheal intubation and death occurred in 11 and 4 cases, respectively. They concluded that the endoscopist-directed administration of propofol appears to result in a lower mortality

rate than that of traditional sedation with benzodiazepines and opioids and a comparable rate to that of general anaesthesia administered by anaesthesiologists.

Nurse-administered propofol sedation for endoscopic procedures is safe when performed by personnel properly trained in airway handling and sedation with propofol and has considerable advantages compared with conventional sedation for endoscopy[106].

Finally, in a very recent study assessing the current use of propofol during colonoscopy screening in 29 countries, it was found that non-anaesthesiologist-administered propofol was used by 29.9% of respondents in 9 countries. Approximately 2/3 of the other endoscopists reported that they would consider implementing non-anaesthesiologist-administered propofol in low-risk patients. It was also found that propofol, benzodiazepine plus opioids and benzodiazepine alone were used in 45%, 31% and 14% of cases, respectively. Importantly, the main reasons for not considering non-anaesthesiologist-administered propofol implementation were medico-legal issues and cost[107]. We suppose that these issues have not been solved and will continue to be discussed in the future.

Should sedation be administered only by a specialist anaesthesiologist?

It is well established that most of the complications occurring during GI endoscopy, such as hypoxemia, hypoventilation, airway obstruction, apnoea, arrhythmias, hypotension and vasovagal episodes, are not related to the procedure itself, but rather to sedation. A recent trial compared endoscopist-administered propofol sedation for colonoscopy with anaesthetist-administered deep sedation. It was found that endoscopist-administered propofol sedation for colonoscopy yielded a better level of satisfaction and patient willingness to undergo further colonoscopies under the same conditions, as well as fewer side effects than anaesthetist-administered deep sedation[108].

Guidelines concerning the use of propofol have been delivered by most major endoscopic associations worldwide. The guidelines of the Endoscopic Section of the German Society for Digestive and Metabolic Diseases suggest that "for simple endoscopic examinations and in low-risk patients, sedation with propofol should be induced by a properly qualified physician and can then be monitored by an experienced person with appropriate training. The person must not have any other tasks while monitoring the sedation". Furthermore, they suggest that an anaesthesiologist should be required only in patients with a high-risk profile.

Four major United States GI Societies, the American Association for the Study of Liver Disease, American College of Gastroenterology, American Gastroenterological Association and American Society for Gastrointestinal Endoscopy, suggest that the administration of propofol is comparable to that of standard sedation with benzodiazepines by non-anaesthesiologists with respect to their safety and efficacy profile.

The guidelines of the European Society of Gastrointestinal Endoscopy, the European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology (produced by 32 individuals from 12 countries, published in 2010) can be summarised as follows:[109] "The consensus suggested that endoscopists and nurses with appropriate training can safely and effectively administer propofol to low-risk patients undergoing endoscopic procedures".

Therefore, the safety profile of non-anaesthesiologist-administered propofol sedation for GI endoscopy seems to be equivalent to that of standard sedation with respect to the risks of hypoxemia, hypotension and bradycardia in ERCP and EUS. Concerning upper and lower GI endoscopy, ERCP and EUS, the time for sedation induction and the recovery time using non-anaesthesiologist-administered propofol sedation are shorter compared with those associated with standard sedation, while non-anaesthesiologist-administered propofol sedation is most likely more cost-effective than standard sedation for ERCP and EUS.

However, the opinion of almost all anaesthesiology societies concerning the use of propofol by non-anaesthesiologists is definitely negative. They emphasise the fact that the manufacturers of propofol restrict its use solely to personnel trained in general anaesthesia and that the United States Food and Drug Administration denied a petition by gastroenterologists seeking the removal of this particular restriction. In a recent consensus statement, the European Society of Anaesthesiology, together with 20 European national anaesthesiology societies in Europe, published new guidelines, entitled "Non-anaesthesiologist Administration of Propofol for Gastrointestinal Endoscopy". They stated that due to its significant risks, propofol should be administered only by those trained in the administration of general anaesthesia[110]. Again, this is a topic of continued debate. International consensus by the major endoscopy societies of the world is urgently needed.

CONCLUSION

Currently, both diagnostic and therapeutic endoscopy is well tolerated and accepted by both patients and endoscopists due to the application of sedation by most centres in the world. During the last 15 years, dramatic changes have occurred in endoscopic procedures, mainly with regard to the sedation techniques and the sophisticated endoscopic instruments and equipment utilised. Today, a large number of drugs are available for achieving successful moderate and deep sedation, and other substances are in the clinical evaluation stage. Moderate sedation using midazolame and an opioid represents the standard method of sedation, although propofol is being increasingly used in many countries. We suggest that the use of this drug will be accepted by an increasing number of endoscopists and that it could become the

preferred sedation agent in the near future. Today, midazolam remains the benzodiazepine of choice, while the most popular opioids are pethidine and fentanyl. Safe sedation in special clinical circumstances, such as in obese, pregnant, and elderly individuals, as well as in patients with chronic lung, renal or liver disease, requires modification of the drug doses used for sedation. It is also crucial for endoscopists to be very familiar with the drug or combination of drugs that they are using in everyday clinical practice. However, the controversy regarding the administration of sedation by an endoscopist, anaesthesiologist or an experienced nurse continues. We emphasise that sedation under the supervision of a properly trained endoscopist could become the standard practice. Due to the legal issues related to the occurrence of unwanted effects of sedation, an updated international consensus regarding the use of sedative agents, especially propofol, is urgently needed.

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