Chapter 28
Sedation for Gastrointestinal Endoscopy: Gastroenterologists Perspective

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Abstract Over the past decade the interest in sedation for gastrointestinal endoscopy has increased worldwide.

A logical consequence was the subsequent development of national guidelines to increase patients safety [1–3]. Comparing the current survey results for sedation from different countries [4–8] with older surveys, shows a significant increase in sedation frequency and the use of ultra – short-acting propofol However, sedation for endoscopy is still the subject of many discussions, which are in part controversial.

One major aspect is the exact indication for sedation, as is not necessary for all gastroenterological endoscopic interventions. Whether sedation is required, depends on the type of examination, duration, complexity, invasiveness, as well as the individual patient's characteristics. However, sedation can make the examination more comfortable for the patient as well as the examining physician. Often it is sedation that makes a successful and low risk examination possible. This is true especially for complex therapeutic interventions [1]. Patients safety as the main goal was the primary concern of the development latest published and updated international guidelines [1, 2]. While in some countries sedation might only be performed by anesthesiologists, sedation by non-anesthesiologist physicians (i.e., gastroenterologists) or a well-trained nursing staff became the standard procedure in low risk patients undergoing gastrointestinal endoscopy [1, 2]. This article provides an overview on patients best preparation, including individual risk stratification, currently most common used sedatives (especially under consideration of the increasingly employed short-acting propofol). In addition, personal and personnel-requirements, as well as technical requirements needed for sedation in gastrointestinal endoscopy are summarized.

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Preparation and Pre-endoscopic Risk Assessment

Sedatives and analgesics might induce overlapping sedation states, ranging from minimal sedation (so called anxiolysis) to general anesthesia [9] (Table 28.1). Therefore, the individual cardio-respiratory risk assessment needs to be carried for any patient [1, 2]. It should include a detailed history asking for the following aspects [1, 2]:

1. Diseases of the cardiovascular and respiratory system,
2. Stridor, snoring, sleep apnea syndrome
3. Complications on previous occasions when sedatives/analgesics, regional and/or general anesthesia were administered
4. Drug allergies, current medication, and possible drug interactions
5. Most recent meal: when and what was eaten
6. Tobacco, alcohol, drug consumption

Table 28.1 Stages of sedation

	Minimal (anxiolysis)	Moderate	Deep	Anesthesia
Reaction to being addressed	Patient reacts appropriately to verbal commands	Somnolence, reaction to louder commands with additional tactile stimulation if necessary	Somnolence, hard to wake, purposeful response after repeated or painful stimulation	Patient cannot be woken, not even in response to pain stimuli
Spontaneous breathing	Not influenced	Adequate	The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway. Spontaneous ventilation may be inadequate.	Inadequate, ITN or larynx mask necessary

Modified from the American Society of Anesthesiologists [9]

Also a physical examination should be performed including vital signs and auscultation of heart and lung to indent potential cardio-respiratory problems that might occur during the procedure. A generally related classification is represented by the so-called ASA classification [9] (Table 28.2). Patients in ASA-class III or higher are known to have an increase risk due to sedation for gastrointestinal procedures. In addition, anatomical features are taken into account. A restricted mouth opening (classified according to the Mallampati score) might complicate the management of respiratory complications [1–3]. Such high risk patients are not suitable for sedation by trained nurses. In this situation one should consider to consult an anesthesiologist [1–3]. It is obligatory to provide appropriate emergency medicines and equipment such as defibrillator, equipment for airway management (bag-mask ventilation, endotracheal intubation) etc. [1–3]. Of course, should the endoscopy team also be familiar with the technique of cardiopulmonary resuscitation, refreshing it regularly as part of structured simulator courses [1–3].

Latest guidelines [1, 2] recommend a routine oxygen administration via a nasal cannula (for example with 2–3 l/min). This is based on the knowledge of the increased occurrence of hypoxemia, particularly at interventional or longer lasting procedures or in patients with high co-morbidity, pulmonary impairment or with circulatory depression (e.g., emergency cases). The administration of oxygen starting at least 2 min before the examination can significantly reduce the frequency of severe hypoxia during the endoscopic procedure [1]. If there is a pronounced hypercapnia, such as COPD, the oxygen supply must also be individually adjusted in order not to reduce the respiratory drive (by excessive O2 supplementation) [1]. The guideline of the American gastroenterologists [3] does not recommend routine prophylactic administration of oxygen. Reason is the feared delay the detection of hypoxia. However, the majority of anesthesiologists believe that the benefits of pre-oxygenation outweigh this disadvantage [1, 2].

Intra-endoscopic Monitoring

Since the transitions between the various stages of sedation (Table 28.3) are fluid, an appropriate patient monitoring is required for all patients by an independent appropriately trained person not involved in the endoscopic procedure [1–3]. The person in charge of monitoring *clinically* checks breathing by observation, palpation of thorax and abdominal wall movement, and possibly palpation of expiratory airstream.

Table 28.2 ASA classification

Grade I	Healthy individual
Grade II	Mild disease, not limiting daily activities
Grade III	Severe disease, limiting daily activities
Grade IV	Severe disease, life-threatening

Table 28.3 Guideline recommendations for sedation with propofol

Guideline, year	NAPS allowed	Limitations for NAPS	Indication for MAC
SAGES, 2009	n.a.	n.a.	ASA > III
ASGE, 2008	Yes (monitored by the doctor)	n.a.	ASA ≥ III, Emergency and complex procedures, in cases of airway difficulties
AGA, 2007	Yes	n.a.	ASA > III, high-risk patients, complex procedures
GSDMD, 2009	Yes	ASA > II, complex procedures, in cases of airway difficulties	ASA ≥ III **and** complex procedures **or** cases of airway difficulties
CAG, 2008	Yes	None	ASA ≥ III, complex procedures, in cases of airway difficulties
ASGH, 2007	Yes	None	n.a
SSGE, 2006	Yes	Complex procedures	ASA ≥ III and deep sedation. Expected difficult airway management

SAGES Society of American Gastrointestinal and Endoscopic Surgeons, *ASGE* American Society of Gastrointestinal Endoscopy, *AGA* American Gastroenterological Association, *GSDMD* German Society for Digestive and Metabolic Diseases, *CAG* Canadian Association of Gastroenterology, *ASGH* Austrian Society of Gastroenterology and Hepatology, *SSGE* Spanish Society of Gastrointestinal Endoscopy, *NAPS* Nurse administered propofol sedation, *ASA* American Society of Anesthesiologists, *MAC* Monitored anesthesia care

Standard-Monitoring recommended by different international societies includes continuous pulse oximetry and automated noninvasive blood pressure measurement (at baseline and then at 3–5-min intervals) during both NAAP and the recovery period; continuous electrocardiography is recommended in selected patients with a history of cardiac and/or pulmonary disease. Baseline, minimum and maximum heart rate/blood pressure, as well as baseline and minimum oxygen blood saturation should be recorded [1–3].

Principal Options for Sedation

Benzodiazepines

Diazepam is nowadays used very rarely because of its long half-life of 25–30 h, according to a first survey in Germany its application was stated only by around 8 % of respondents [5]. In contrast, about 80 % of respondents use midazolam [5]. Its pharmacological advantages are a shorter half-life (1,5–3 h), a better retrograde amnesia and a higher water solubility. Compared to diazepam patient tolerance and sedation efficiency are consistently well [1]. A combination of benzodiazepines and

opioids (predominantly midazolam plus meperidine) was used in about one third of all gastroenterologist for colonoscopy [5]. The use in diagnostic endoscopy of the upper digestive tract (e.g., diagnostic EUS), however, is considered obsolete [5]. The advantage of a combination of benzodiazepines and opioids at endoscopy is highly controversial and can be seen rather negatively according to recent data [1, 2].

Propofol: The New Standard

Prerequisites

With respect to the introduction of the short-acting propofol (plasma half-life of 7–8 min) legal and personnel requirements are still the center of discussion. Numerous guidelines for sedation in endoscopy [1–3, 9–16], were counted in the last years worldwide, their recommendations for the use of propofol are summarized in Table 28.3. All guidelines are uniform on the assumption that the endoscopist themselves can not perform the endoscopic procedure, patient monitoring and propofol administration at the same time. Demanded is therefore a further, independent assistant person not involved in the endoscopic procedure. This can be a qualified caregiver (so called NAPS, "nurse administered propofol sedation") a second specialist in internal medicine or a gastroenterologist (usually called " gastroenterologist -directed propofol sedation, G-DPS ") or an anesthesia team ("monitored anesthesia care, MAC"). While in principle all guidelines advocate "MAC", they differed with respect to the recommendation when the gastroenterologist should consider the use of anesthesia mandatory (Table 28.3). Provided however, is that the patient is monitored according to the rules of science and that for any incident the necessary personal and instrumental equipment is given [1–3]. The qualification of medical and non-medical personnel should be maintained by regular participation in structured training curricula as developed on national [17] or European basis [18] ensuring to comply with this legal requirement in different countries and again to meet the personal requirements postulated. This is of course not only in addition to the use of propofol, but also for the use of other substances for sedation or analgesia. While currently only isolated special training guidelines exist on premedication and management of emergency situations, it could have shown that specific training courses, such as those based on simulators, might improve physicians' confidence in handling emergency situations [19].

Diagnostic Endoscopy

Propofol has the distinct advantage of sedation compared to benzodiazepines, that the effect occurs much faster [20] and patients recover more rapidly [21–30]. This also applies to the regeneration of psychomotor functions, when propofol was compared with gastroscopy or colonoscopy with a combination of midazolam and meperidine

by using a driving simulator [23]. Similar results were published by a study from Japan comparing propofol with midazolam for EGG [31]. The possible improvement of diagnostic accuracy in the EGD appears an additional advantage of propofol compared to midazolam in a randomized controlled trial by Meining et al. [32].

Interventional Endoscopy

Regarding sedation with propofol the investigators evaluated the patients acceptability and tolerance for both the gastroscopy and colonoscopy, as well as for the ERCP in comparison to benzodiazepines as better [24, 25] or equally well [21, 33, 34]. In particular, for interventional examinations such as ERCP also a significantly better patient cooperation could have been shown [26, 27, 35]. Especially with the use of propofol for interventional studies one has to consider that this is not entirely without risk, as shown by data on a risk factor analysis [36]. Of 9547 patients who received propofol sedation, during the interventional upper endoscopy (EGD, ERCP, EUS) over a period of 6 years, 3151 patients received propofol as monosedation and the remaining 6396 a combination of propofol and midazolam. There were a total of 135 serious complications, premature termination of the procedure had to be made in 1.4 %. In 40 patients (0.4 %) a short-term mask ventilation and in nine patients (0.09 %) endotracheal intubation was necessary, another eight patients (0.08 %) had to be monitored on the ICU. Four patients died (mortality rate 0.03 %), in three cases potentially sedation associated side effects must be considered. As independent risk factors for the occurrence of cardiorespiratory complications emergency examinations and a higher dose of propofol were identified [36].

Risk Patients: Propofol or Midazolam?

Both during the investigation and in the post-intervention phase under midazolam elderly patients are at increased risk of documented hypoxemia [37, 38]. In the elderly, it is therefore appropriate to reduce the dose of midazolam [39]. This also suggests the modification of the recommendations of the American Society of Gastroenterology for older patients undergoing gastrointestinal endoscopy [40]. In addition, substances with low cumulative dose [40, 41] should be preferred. The careful use of propofol due to its pharmacokinetic is even safe for high-risk patients aged over 85 years, as we could have shown in a randomized trial comparing propofol with a combination of midazolam and meperidine for ERCP [37]. Similar findings were obtained in a study by Heuss et al. [42]. Since cardio-respiratory events tend to occurred more frequently, there need to be increased care in these patients. Patients with liver cirrhosis are another risk group, where a hepatic encephalopathy may increase under midazolam [43–46]. This can lead to an unforeseen anesthetic stage during sedation, a prolonged wake up period with reduced psychomotor skills.

In randomized controlled trial comparing midazolam with propofol for sedation in patients with liver cirrhosis undergoing interventional EGD the mentioned side effects did not occur when using the ultra-short acting propofol [46].

Propofol and Midazolam (So-Called Balanced Sedation)

The propofol dose required can significantly be reduced "co-induction" with small amounts of midazolam (usually 2–3 mg) [30, 47], what particularly in often prolonged interventional endoscopic procedures is possible and valid only for this. For short duration procedures, most of which are diagnostic, should be dispensed with a co-induction with midazolam, because the savings effect is only insignificantly. In addition, the advantage of rapid psychomotor recovery when using propofol as a single agent [23] and the associated possibility of faster release should not be forgiven (discharge from the recovery room to the ward or outpatient examinations) in these cases.

Propofol Plus Midazolam or Opiates

Cordruwisch et al. [48] performed sedation in 64 patients, who underwent two successive, prolonged (>30 min) endoscopic examinations following up each other. In the first procedure sedation was performed with propofol and in the subsequent examination with a combination of midazolam and propofol. The combination had the advantage of a considerable saving effect of 59 % propofol. However postinterventional wake up was twice as long as in the propofol mono-sedation group (8 min versus 4 min). Van Natta et al. [49] examined in another randomized study 200 patients who received sedation with propofol either alone, propofol plus fentanyl, propofol plus midazolam or midazolam plus fentanyl. By combining process thereby moderate sedation with a shorter recovery time was reached. On the other hand correspondingly higher doses were required with sole administration of propofol, which induced a higher sedation depth leading to a substantially longer recovery time.

Propofol and/or Opiates

Akcaboy et al. [50] studied in a randomized trial in 100 patients during a colonoscopy, the sole administration of the short-acting analgesic drug remifentanil compared to mono-sedation with propofol. It was shown that remifentanil achieved an adequate sedation, amnesia and compared to propofol better analgesia. An increased incidence of nausea and vomiting during the recovery reduced this advantage,

however, significantly. Moermann et al. [51] investigated the additive dose of remifentanil for sedation with propofol in a randomized double-blind trail in 50 relatively healthy patients (ASA I and II) undergoing colonoscopy. The combination of remifentanil and propofol showed significantly more often a decrease in blood pressure and oxygen saturation. By administering remifentanil the dose of propofol required could have been reduced, however, the recovery time under propofol mono-sedation was significantly shorter ($p < 0.01$) and patients significantly more satisfied ($p < 0.01$).

Propofol by Non-medical Assistants

The first major studies of propofol bolus sedation by assistants in colonoscopy from the United States and Switzerland respectively included more than 2000 patients [52, 53]. No patient need to be intubated endotracheal and only in 0.2 % of cases a temporary mask ventilation was required. According to these studies, such an approach has also been discussed in other countries (e.g., Germany, Austria, Switzerland) increasingly as an alternative method. An important role was played certainly the increasing cost pressure in the health care system and the associated cost reduction for individual examination [54]. The doctor who initially introduces and delegates to the assistant staff must be informed necessarily in each individual case on the patient, i.e., for example, history and premedication, physical status etc. He/she must also regularly check on the qualifications of the assistant staff personally and assume the sedation and the resulting complications full responsibility. Appropriate training curricula e.g., on the basis of the German or European curriculum [17, 18] should be developed under consideration of different legal aspects for other countries. However, these courses are just a basic course which initially only provides a technical qualification. The practical skills should then be drawn up, for example as part of a study visit.

In some countries (e.g., France and in most states of the US) the administration of propofol is restricted by law to anesthesiologists, therefore, rendering the use of NAPS or even G-DPS impossible.

Alternative Methods

Rudin et al. were able to show in a meta-analysis [55] that the use of music in endoscopy ($p = 0.001$) and the sedatives by 15 % ($p = 0.055$) could contribute to a reduction of the dose of analgesics used to 29.7 %. Also sedation induced cardio-respiratory complications could be minimized by minimal sedation or through the use of ultrathin endoscopes as well as the complete renunciation of sedation [56, 57].

A simple analysis of brain wave activity within the neuromonitoring during sedation for endoscopy can now be performed by using the bispectral index (BIS monitoring) or by using the Narcotrend® process. Numerous studies in the past decade have proven that such EEG monitoring during endoscopy by 3–5 placed on

the front side of the head of the patient electrodes is possible. The majority of studies, however, showed no clear advantage over the standard monitoring. Meanwhile occupy several randomized controlled trials for ERCP or performing an ESD on stomach a significant reduction in the required dose of propofol [35, 58–60]. Besides a shorter recovery time, however, these trials did not demonstrate a decisive safety advantage

Post-procedure Care

When a patient can be discharged after sedation, is already regulated since the 90s by the minimum criteria that apply regardless of the substance used [9]. These demands include stable vital signs and a complete or substantial pain relief. The patient should also drink liquids without difficulty, walk unaided and be able to control urination and are modified for more practical application [1, 2]. If necessary, the doctor should inform the patient again to the typical signs of complications. In any case it is recommended that the patient must be accompanied by another person with and to make sure of the possibilities for adequate follow-up at home. However, these discharge criteria, mainly focusing on vital signs of patients immediately after sedation, while cognitive functions and psychomotor skills are in this case not be evaluated. Even discharge criteria such as the Aldrete score [61] mainly focused on cardiovascular and respiratory functions, but may not ultimately reflect the psychomotor skills of the patient at discharge. Even though a maximum discharge score is achieved with 60–70 % of the initial value, the psychomotor skills are often significantly limited, as Willey et al. [62] were able to demonstrate in a study using midazolam in combination with pethidine for EGD. A good option is therefore the currently recommended use the use of ultra-short-acting substances as a single agent [1, 2]., because the limitation period of psychomotor functions and the half-life of the substances used are closely related. These skills recover faster after propofol compared to midazolam (possibly plus pethidine) as we [23] demonstrated in 96 patients after routine gastroscopy and colonoscopy in a driving simulator study. Under Midazolam, optionally in combination with pethidine, psychomotor skills were significantly limited 2 h after the sedation, while patients after propofol sedation showed skills comparable to their baseline performance. Finally, to clearly define the period after which patients might lead a motor vehicle safe again, would require large-scale “on-the-road” studies under well defined primary outcome parameters. Current results from simulator tests are only surrogate parameters here. Furthermore, our results refer exclusively to a mono-sedation with propofol. The effects of the combination of commonly used midazolam and propofol on the mileage, however, are not yet been investigated. The half-life of the substance used and the used sedation regimen (propofol as mono-sedation or combined with benzodiazepines or analgesics) is the decisive criterion for both the first passive on the road, and for the period of incapacity. Patients co-morbidity as well as and further individual patients factors (e.g., employment as a traffic pilot) should also be considered

[63, 64]. Usually, the patient will be able to drive, to work and to engage in legally binding decisions the next day (current European guidelines recommend a 6–12 h interval for propofol use only) [1, 2]. Strictly not recommended is the routine antagonize midazolam, for example by flumazenil to allow an earlier discharge from hospital or medical practice. The risk in this case is a relative safety for the patient, because it is first well monitored. However, the half-life of flumazenil is substantially shorter than that of midazolam and its metabolites. Thus there is a clear risk that delayed respiratory depression or an impairment of cognitive or psychomotor skills occur. Should the use of flumazenil for clinical reasons are required, the patient must be monitored for longer [1].

Conclusion for Practice

Before planning the use of sedation the cardio-respiratory risk needs to be estimated individually. A complete and fully functional emergency equipment and a team trained in airway management and resuscitation must be available. The routine prophylactic administration of 2 l of oxygen via a nasal cannula is recommended to avoid hypoxemia after any contraindications have been excluded. For purely diagnostic examinations the benefit of sedation is not clearly documented, however standard at therapeutic intention. Numerous studies have now confirming superiority of propofol compared to benzodiazepines in endoscopic interventions with an increased use in many countries. Although guidelines support the use of propofol by non-anesthesiologists, it remains not permitted in some countries. A significant advantage of propofol in purely diagnostic examinations is the rapid recovery time, also improved diagnostic accuracy seems possible. In most cases of prolonged interventional endoscopies, the advantage lies in improved patient cooperation. Propofol is safe in patients liver with cirrhosis, as well as in older high-risk patients when used carefully. A co-induction with midazolam can significantly reduce the dose of propofol, which might be required in selected patients undergoing long lasting procedures. In short procedures the disadvantage of impaired psychomotor function outweighs. The sole administration of short acting opiates instead of propofol has no advantage and is limited by their side effects such as nausea and vomiting. Sedation with propofol can safely be performed by non-anesthesiologists and might be delegated to well trained nursing staff under well defined conditions (in low-risk patients and simple procedures) in some countries. Monitoring procedures as capnography and neuro-monitoring is currently not among the standard methods and have been able to show no relevant influence or even advantage in terms of patient safety. At discharge minimum criteria should be met. In particular, patients should leave due to the current legal situation and the medical duty of care the endoscopy unit after sedation in accompaniment. It is advisable to address the organization of an accompanying person in the first explanatory meeting. The passive and active use on the road, as well as the duration of incapacity depend on the half-life of the substance used.

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