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Review

Sedation in Gastrointestinal endoscopy Part 2

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SUMMARY

Best sedation practices for interventional gastrointestinal endoscopy involve the consideration of many patients' factors, including age, medical history, clinical status, level of anxiety as well as physician's access to anaesthesia support. Conscious sedation itself would lead to serious complications, even to mortality in non-skilled hands or in not well organized units. The increasing technical complexity of the endoscopic procedures frequently requires deeper levels of sedation, which can be advantageous for patient comfort and for achievement of higher quality procedures, especially in children and elderly patients who are difficult to cooperate with.

Keywords: Intervantional endoscopy, lower gastrointestinal tract, endoscopy, conscious sedation

COLONOSCOPY

Colonoscopy is basic to the investigation of lower GI tract disorders. As pain and vasovagal reactions are common during the procedure, administration of sedation and analgesia is imperative.[1]

Techniques of sedation must guarantee the comfort and safety of patients, as well as rapid recovery to enable discharge from the endoscopy unit as soon as possible.[2]

Moderate sedation, deep sedation, general anesthesia, inhalation of nitrous oxide and alternative methods such as acupuncture, use of relaxation music and hypnotherapy have been used.[3]

While in some countries gastroenterologists use sedation only in difficult cases of colonoscopy, others use deep sedation or general anesthesia. Moderate sedation is the most widely used method for colonoscopy.[4,5] This level of sedation is appropriate when provided by a combination of an opiate and a benzodiazepine.[6] The usual combinations used in this setting are midazolam with meperidine, and midazolam with fentanyl. Meperidine has longer duration of effect and increased incidence of post-procedural nausea and vomiting, compared with fentanyl. Meperidine has active metabolites that cause seizures when accumulated. Fentanyl can cause muscle rigidity as well as thoracic rigidity that could impair ventilation. Although the combination of benzodiazepine and opioids is thought to be safe and acceptable even in the anesthesiology community, Patel et al demonstrate that deep sedation occurs frequently during elective endoscopy with meperidine and midazolam.[7] More specifically, among 80 patients studied undergoing endoscopic procedures in the GI tract, 54% passed into a state of deep sedation and 11% of them were colonoscopies. One explanation could be the synergistic effect caused by the combination of these medications. Thus, the recommended initiation of sedation would be Ό of the dose of opiate being given as mono-therapy, followed by (10 min later) titration of the benzodiazepine according to the patient need.[8] The addition of diphenydramine as an adjunct to sedation for colonoscopy improves sedation.[9]

Despite satisfactory comfort, for most patients a combination of midazolam with opiates is not ideal. The above combination causes synergistic sedation and increases the likelihood of ventilatory depression.[7,10] The duration of the effects of this combination is usually longer than the time required for the procedure, and their use requires prolonged recovery, resulting in delayed hospital discharge.[11]

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Because colonoscopy requires rapid turnover of patients, an agent with rapid onset and offset of action, and convenient titrability of anesthetic/analgesic depth would be ideal. Over the last few years, there has been growing interest in the use of short acting agents like propofol or remifentanil during endoscopic procedures.[12-15]

The advantages of propofol compared to benzodiazepines and narcotics are directly related to its properties: a more rapid onset of action, full relief from discomfort and rapid recovery to alertness without residual sedative effects or imponderable anterograde amnesia. As most endoscopic units are coming under increasing financial pressures, economic arguments for improved efficiency like faster patient discharge or reduction of procedure time, are important factors cited in the rationale for using propofol in routine endoscopy. Propofol patients also report a higher degree of satisfaction compared to benzodiazepine patients.[16] Propofol has been used as a sole agent or in combination with benzodiazepines or narcotics during colonoscopy.[17-19] The combination of propofol with a benzodiazepine has been primarily used to ensure deep sedation[20] or to reduce the required quantities of the rather expensive propofol.[21]

The combination schemes prove to be more efficient in targeting conscious sedation. In a 1999 review, Lazzaroni et al mention that anaesthesiologists have used propofol in combination with low dose of midazolam, fentanyl and alfentanil to produce effective sedo-analgesia.[22] However non-anesthesiologists need to be extremely worried of this sort of practice, since propofol acts synergistically with both midazolam[23] and alfentanil.[24]

Reimann and colleagues used propofol in combination with benzodiazepines rather than an opioid.[21] Their paper reports a study of 79 patients undergoing colonoscopy who were randomly assigned to receive either midazolam, with or without nalbuphine (group I); or midazolam (2 mg) and repetitive increments of propofol (group II). Unsurprisingly, patients in group I required a relatively large dose of midazolam (mean dose 9 mg), and 59% subsequently needed additional analgesia with nalbuphine (mean dose 20 mg) to ensure completion of the colonoscopy. Equally predictable was group II in the synergistic sedation group, who received only 2 mg of midazolam and a relatively modest dose of propofol, recovered much sooner after the procedure (mean 17 min) compared with group I (mean 93 min).

In another study by Paspatis et al[11] a total of 120 consecutive patients undergoing colonoscopy in a prospective study were randomly assigned to receive either midazolam plus propofol (group A) or midazolam with pethidine (meperidine). The results of this study suggest that synergistic sedation with a low dose of midazolam combined with propofol was superior to a standard combination of midazolam and the opioid pethidine for colonoscopies as far as patient comfort and recovery times are concerned.

Although propofol has been widely used during colonoscopy, it is not an innocuous medication. It is more dangerous than the traditional sedative agents. The principal and most important risk of propofol use is its narrow therapeutic range. This poses the danger that patients might inadvertently slip into a state of deep sedation or general anesthesia with concomitant impairment of spontaneous ventilation. In contrast to benzodiazepines, no reversal agents, such as flumazenile, is available, and patient resuscitation must be carried out using the jaw thrust maneuver, positioning of a nasopharyngeal tube or even positive pressure bag ventilation. Due to the short duration of effect, this intervention is fortunately required for only a few minutes. Nevertheless, endoscopists must be aware of this potential danger and alert themselves to any prolonged period of apnea.[25] It is therefore essential that those administering propofol are trained in advanced cardiac life support (ACLS) and airway management. Indeed, in some countries, propofol use is restricted solely to the anesthesiologists.[16]

In the literature, the use of propofol is often associated with deep sedation.[17] It is noteworthy to mention that the level of sedation is primarily dose dependent. When propofol is used as a single substance, the lacking analgesic effect may possibly lead endoscopists to aim for deeper levels of unconsciousness increasing the propofol dose and possibly the related side effects.[16]

Quite often, multiple doses of bolus propofol are required to raise the level of patient tolerance during a colonoscopy. This frequently results in the patient's being obtund and meeting the criteria for deep sedation or even general anaesthesia. This development is not fully predictable, and depends greatly on the patient's physical status, age, and coexisting diseases. There is a very slippery slope between mild sedation and general anesthesia with the use of this drug, even in skilled hands. Anesthesiologists face this clinical challenge day in and day out, and even recent residency graduates have experienced this with thousands of patients.[26]

Anesthesiologists have proposed regimens in which propofol is combined with an analgesic and/or another sedative.[27] Due to the mentioned lack of analgesic properties, the combined use with a pain-relieving drug is ra-

tional. Nevertheless, non anesthesiologists should be extremely cautious of possible side effects since the drugs act synergistically and may cause ventilatory depression.[28] The combination of propofol with an opioid always necessitates a reduction in dosage of propofol.[29] A long acting opioid (such as pethidine) can be administered in advance[8] but ideally, the profile of effect of the administerd drug should be comparable and not abolish the benefits of propofol. From this point of view, the combination with a very short-acting (and highly potent) opioid, such as alfentanil or remifentanil would make sense for painful procedures.[24,30]

One rarely-cited benefit regarding propofol's safety is that the major negative effects of the drug develop concurrently with when the most attention is being focused on the patient. Therefore, any alteration in physiologic parameters can be detected immediately. This stands in contrast to benzodiazepines where active metabolites may have their largest effect after cessation of endoscopic procedure.[31] As a result, patients having received benzodiazepine sedation may experience a delayed desaturation and hypoxemia in the recovery area, when they are not under close attention.

Remifentanil during colonoscopy has been used alone[24,31,33] or in combination with propofol.[34] Very few studies have investigated the use of remifentanil as a single agent for monitored anesthesia care during colonoscopy.

In these studies, remifentanil has been compared with propofol.

The use of remifentanil as a sole agent during colonoscopy has been investigated in the study by Manolaraki et al[24] and compared with the sedative scheme midazolam plus pethidine. In this study, the authors tested the hypothesis that if pain relief was adequate during colonoscopy, sedation would no longer be required. This hypothesis was originally introduced by Moerman et al.[32]

In the study by Manolaraki et al,[24] the authors compared remifentanil with the sedative combination of benzodiazepines plus opioids. Use of remifentanil in endoscopic units might have advantages over other drugs because of its profound analgesic effects, rapid onset and offset time, rapid titration to the individual patient's requirements, and intermittent pain during colonoscopy.[32,33] In this study the authors concluded that remifentanil during colonoscopy provides sufficient pain relief with better hemodynamic stability, less respiratory depression, and significantly faster recovery and hospital discharge than moderate sedation with midazolam and pethidine.[24]

Moerman et al[32] compared remifentanil and propofol for MAC (Monitor Anesthesia Care) during colonoscopy. In this study, remifentanil provided efficient pain relief, faster recovery of cognitive functions, and a smoother hemodynamic profile than propofol when administered by trained professionals. Additionally, they reported a significant difference in patient satisfaction; it was significantly higher in the propofol than in the remifentanil group.

In the study of Bouvet et al,[33] remifentanil and propofol were used for patient-control analgesia (PCA) during digestive endoscopic procedures. The authors concluded that self-administration of remifentanil is as effective as self administration of propofol.

A relative new -under development- sedative agent for colonoscopy is a propofol prodrug, Fospropofol.[35,36] Blood levels of propofol after administration of fospropofol reach lower peak levels and are more sustained than after administration of intravenous propofol. This effect creates ease of administration, because in short-duration endoscopic procedures, such as colonoscopies, patients may only require a single dose of fospropofol. To improve pain control and to facilitate targeting moderate sedation, fospropofol is co-administered with a narcotic, typically fentanyl. A major potential advantage of fospropofol is that the drug manufacturer is seeking approval from the Food and Drug Administration for administration by non-anesthesiologists.

In conclusion, training in endoscopic sedation is the most important factor for a safe and successful completion of a colonoscopy. It remains to be seen whether propofol or other power sedative new drugs like fospropofol gain the necessary approval to be administrated by non-anesthesiologists.

Sedation in ERCP and EUS

ERCP and EUS are advanced endoscopic procedures that are more complex compared with colonoscopy and EGD. Because these procedures last longer than usual, endoscopies of the GI tract often cause lack of patient tolerance and cooperation.

In recent years, ERCP has almost solely been used for therapeutic purposes. As a result, many ERCP procedures like intrahepatic stone removal, stent placement or ERCP in patients with Billroth II operations present great difficulty and risk.[37]

EUS with or without FNA is a lengthy procedure, the instruments used are broader than conventional ones with a bulky and stiff tip (edge) so the procedure is accompanied

by comparatively greater patient discomfort. Aside from being used for diagnostic purpose, EUS is used for therapeutic purposes like cyst diversion or stent placement.[38]

The success of the above endoscopies is widely attributed to adequate patient cooperation. In such cases, good quality of sedation is of great importance. Compared with colonoscopies and EGDs which are usually performed with moderate sedation, ERCPs and EUS are usually completed with deep sedation.[39]

A combination of benzodiazepines and opiates, the medication used most commonly by gastroenterologists, provides adequate analgesia and sedation during ERCP and EUS. Midazolam and pethidine are the usual combination regimens that can cause moderate or deep sedation depending on the doses of those medications used and patient age. Despite satisfactory comfort for most patients undergoing ERCP and EUS, a combination of midazolam with opiates is not ideal. The synergistic sedation caused by their combination increases the duration of the effects of these drugs, the likelihood of ventilatory depression and prolonged recovery time.[7,10.11] Moreover, sedation with benzodiazepines is unsuitable for alcoholic and stressful patients as well as for patients with chronic use of benzodiazepines. Endoscopies failed in up to 30% of those patients.[40]

In recent years propofol has been included in lots of gastroenterology units. Originally propofol was used in some endoscopic units under the supervision of anesthesiologists. The quick initiation and recovery of propofol sedation, the easy titration of the drug, the excellent quality of sedation and the patient and endoscopists satisfaction are the most important reasons for propofol use. Moreover, propofol has no active metabolites and undergoes short liver clearance after iv administration, so it does not influence patients in cases of prolonged administration.

The first prospective randomized study about propofol sedation during ERCP comes from Germany.[41] In this study, 99 patients received propofol 40(<60 Kg) or 60(>60 Kg) mg bolus and 20 mg bolus doses without up limitation. Ninety-eight patients received midazolam (2.5 mg bolus) and up to 10 mg supplemental doses. Propofol caused a more rapid onset of sedation than midazolam. Mean recovery times as well as the recovery score were significantly shorter with propofol. Propofol provided better patient cooperation than midazolam but procedure tolerability was rated the same by both groups of patients. Changes in vital signs were observed at comparable frequencies with temporary oxygen desaturation occurring (<85%) in 6 patients in the propofol group and in 4 patients receiving midazolam (not significant). An episode of apnea had to be managed by mask ventilation via an ambu bag (lasting 8 min) in one of the patients receiving propofol sedation. The conclusion of this study was that propofol sedation in ERCP is more effective than midazolam, safe under adequate patient monitoring and associated with a faster post-procedural recovery.

In another study by Junk et al,[42] 80 patients were randomized to sedation with propofol or midazolam during ERCP. Midazolam was given by the endoscopist and titrated to the patients' response to a maximum dose of 15 mg per patient. In the propofol group an anesthesiologist administered the propofol at an initial bolus dose of 0.5-3 mg/Kg and then at a rate of 4-8 mg/Kg/h according to the desired sedation level. As in previous studies recovery times were significantly shorter. The endoscopists and the patients both judged the quality of sedation to be better in the propofol group. It is important to point out that in 1/5 of midazolam sedated patients the procedure was not completed by midazolam as the sole agent. There were no differences in blood pressure, pulse, or oxygen saturation between the two groups. One patient in the propofol group suffered a protracted apneic phase accompanied by hypotension. These complications were managed by manual ventilation and drug therapy. In this study propofol prove to be an excellent sedative for ERCP. Because of the narrow therapeutic window, close patient monitoring is recommended.

In the study by Vargo et al gastroenterologists, trained in advanced cardiac life support, administered propofol or midazolam and meperidine for ERCP and EUS in 75 patients. Monitoring with capnography allowed for rapid titration of propofol at the earliest signs of respiratory depression. Capnography during sedation contribute to better patient monitoring of respiratory activity and allowed for early detection of depressed respiration compared to pulse oxymetry or visual assessment.[25] This study shows that propofol leads to significantly improved recovery of baseline activity and food intake 24 hours after the procedure.

When propofol was administrated in high risk octogenarians,[43] it provided significantly better patient cooperation than midazolam/meperidine, shorter recovery time and lower number of desaturation events.

The first study where a combination of midazolam and propofol was used in ERCP comes from Germany. In this study[44] 239 patients undergoing ERCP or EGD were randomized to receive propofol alone or in combination with midazolam intravenously. The authors concluded that se-

dation with propofol and midazolam requires a lower total dose of propofol, but otherwise has no superior sedation efficacy and is associated with a slower post-procedure recovery than sedation with propofol alone.

The first study where oral midazolam was combined with iv propofol in ERCP, comes from Greece. Paspatis et al randomized 91 patients to receive propofol alone or in combination with 7.5 mg of midazolam per os 30 min before ERCP. The authors concluded that synergistic sedation with midazolam and propofol significantly reduces the dose of propofol required as well as anxiety levels before the procedure.[45]

In an Italian study[46] propofol sedation was commenced by a target-controlled infusion system (TCI). This system automatically adjusts the rate of infusion of propofol to maintain a desired (target) concentration. This study looks into whether administration of propofol with TCI could improve the sedation of patients undergoing ERCP. The TCI system provides safe and effective sedation during ERCP. In this study, an anesthesiologist delivered the propofol.

As regards safety of propofol sedation by registered nurses, a large multicentre study has recently presented data from 36743 endoscopies (782 ERCP and EUS). There were no cases requiring endotracheal intubation or cases resulting in death, neurologic sequelae, or other permanent injury. The rate of respiratory events requiring assisted ventilation ranged from 1 per 500 to 1 per 1000 cases.[47] The conclusion was that trained nurses and endoscopists can administer propofol safely for endoscopic procedures. Nurse-administered propofol sedation is one potential solution to the high cost associated with anesthetist-delivered sedation for endoscopy.

In ERCP and EUS, procedures where deep sedation is usually required, propofol seems to constitute a substitute sedative agent for midazolam.

Sedation in Elderly patients

Geriatric patients are defined as those 65 years of age and over. Advanced age patients are those 80 years of age and over. For patients in any age group, endoscopy should be applied only when the results will materially influence management or outcome. Increased attention should be paid to the risk engendered by age-related diseases, such as cardiac and pulmonary dysfunction. Significant risk may outweigh the acknowledged benefits of a procedure.

Most gastrointestinal endoscopy is performed with the benefit of conscious sedation. A variety of physiologic processes contribute to the increase in sensitivity and risks for conscious sedation in geriatric patients. The aging process is characterized by a progressive decline in organ function beginning in the fourth decade but accelerating during what is traditionally known as geriatric years beyond the sixth decade. Arterial oxygenation progressively deteriorates with age, with or without supplementation. Central nervous system depressants produce greater respiratory depression and a greater incidence of transient apnea and episodic respiration. Basal metabolic requirements and consequent body heat production decline, putting elderly patients at risk for hypothermia during prolonged periods of sedation. The age-related increase in lipid fraction of the body mass yields an expansion of the distribution volume for pharmacologic agents, which are highly lipid soluble, including benzodiazepines. Combined with reduced hepatic and renal clearance mechanisms, this can prolong the recovery of elderly patients after sedation. A complex interplay between heightened CNS sensitivity and alterations in drug receptors, volume of distribution and intercompartmental transfer contributes to the reduced dosage requirements for all of the standard agents used in conscious sedation. Age-related diseases and overly rapid or excessive dosing contribute more to the cardio-pulmonary complications of conscious sedation than does age alone.

The modification in conscious sedation practices in the geriatric population is administration of fewer agents at a slower rate and lower cumulative dose. Midazolam and/or narcotics are generally used. The initial dose should be lower and titration should be more gradual to allow assessment of the full effect at each dose level.[48]

Sedation in paediatric patients

Paediatric endoscopies are usually carried out by paediatric gastroenterologists. Occasionally, paediatric surgeons may be trained in endoscopy. Because children are not simply young adults, optimal performance of endoscopy in these patients requires an adequate knowledge and understanding of paediatrics and a thorough understanding of the child's medical background.[49]

In many practice settings, however, adult endoscopists are called upon to provide advanced therapeutic endoscopic services, such as ERCP and EUS, or basic endoscopic services when paediatric gastroenterologists are unavailable. To provide appropriate care for the child in such circumstances, a team approach is required with the paediatrician or the paediatric gastroenterologist and the adult endoscopist present.

Paediatric patients with presumed normal gastric emp-

tying should be fasted before elective sedation for a minimum of 2 hours after ingesting clear liquids.[50]

The American Academy of Paediatrics guideline on sedation follows the recommendations of the ASA for general anaesthesia and advises fasting from breast milk for 4 hours and from formula, nonhuman milk, and solids for 6 hours before elective sedation.[50] The risks of sedation without appropriate fasting in emergency cases must be weighed against the necessity for the procedure and the expected benefit. In these cases, the lightest sedation able to achieve successful completion of the procedure should be used. Some institutions often have specific preprocedure fasting guidelines. Prolonged fasts without fluids are more difficult for young children, so morning procedures and timely schedules are desirable.

Oral and nasal administration of benzodiazepines is useful for the premedication of paediatric patients before administering IV sedation. Peak serum concentrations and central nervous system effects are reached 10 minutes after intranasal midazolam and about 20 to 30 minutes after oral ingestion. In a randomized controlled trial intranasal midazolam (0.2 mg/kg) significantly reduced negative behaviours during separation from parents, but did not influence tolerance for venipuncture or EGD[51] compared with intranasal saline. Discomfort and irritation from nasal administration largely negated the limited benefit on separation anxiety. Another placebo controlled trial evaluated oral ingestion of 0.5 mg/kg of midazolam in a flavoured syrup (1:1 mixture of 2.5 ml syryp and 2.5 ml injectable midazolam 5mg/ml=end dilution 2.5mg/ml).[52] Oral midazolam significantly improved the ease of separation from parents and of IV insertion, the degree of amnesia for IV insertion, comfort during the procedure, and both patient and parental satisfaction scores. Physiologic monitoring parameters were not altered prior to, during, or after the procedure, and there were no differences in pre-procedure time, dosages of parenteral sedatives, procedure length, post-procedure recovery, or time of discharge. Premedication with oral midazolam has also been shown to reduce the dose of propofol, allows for easier iv-line placement, easier separation from the parents, it reduces pain induced by the iv-line placement, and provides greater patient comfort than a placebo.[15,53]

Most gastrointestinal endoscopy is performed with the benefit of conscious sedation or general anesthesia.[54] Pediatric conscious sedation is most commonly performed using midazolam, with or without fentanyl or meperidine. As in adults, incorporation of midazolam in sedation regimens yields improved amnesia affects in pediatric patients.[55] When Fentanyl is administrated, less midazolam is needed than when meperidine is given with midazolam.[56] Additionally, shorter recovery times occur when fentanyl is used compared with meperidine.

Administration should be weight based and titrated by response, allowing adequate time between doses to assess effects and need for additional medication. Despite anticipated differences in sedative dosages and metabolism, requirements for individual patients may vary significantly, based in part on their psycho-social development and attention to their surrounding environment by the endoscopy team.[57] Frequently, higher doses are ultimately required in the preschool, elementary and pre-teenage groups.

General anesthesia and propofol are commonly used for pediatric endoscopy, usually based upon age or anticipated patient intolerance for the procedure. Some medical centres and paediatric GI practices use general anesthesia and/or propofol exclusively for endoscopy, and this number appears to be increasing.[58]

Other indications may include the complexity of the planned procedure, physician preferences, patient comorbidities, or institutional guidelines. One prospective evaluation noted equivalent efficacy and safety, with markedly reduced costs when using rigorously standardized procedural sedation compared with general anesthesia for performance of endoscopy in children of all age groups.[59] Higher doses of sedation were required in children 3 to 9 years of age, although deep sedation was often reached.

REFERENCES

1. Notini-Gudmarsson AK, Dolk A, Jakobsson J, Johansson C. Nitrous oxide: a valuable alternative for pain relief and sedation during routine colonoscopy. Endoscopy 1996; 28:283-287
2. Sa Rego MM, Watcha MF, White PF. The changing role of monitored anesthesia care in the ambulatory setting. Anesth Analg. 1997; 85:1020-1036
3. Wong RCK. The menu of endoscopic sedation: all you-can eat, combination set, a la carte, alternative cuisine, or go hungry. Gastrointest Endosc 2001; 54:122-126
4. Rodney WM, Dabov G, Orientale E, Reeves WP. Sedation associated with a more complete colonoscopy. J Fam Pract 1993; 36:394-400
5. Rex DK. Review article: moderate sedation for endoscopy: sedation regimens for non-anesthesiologists. Aliment Pharmacol Ther 2006; 24:163-171
6. Keefe EB. Sedation and analgesia for endoscopy. Gastroenterology 1995; 108: 932-934
7. Patel S, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, Conwell DL, Zuccaro G. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. Am J Gastroenterol 2005; 100: 2689-2695

8. Bell GD. Premedication, preparation, and surveillance. Endoscopy 2000; 32: 92-100
9. Tu Rh, Grewall P, Leung JW, Suryaprasad AG, Sheykhzadeh PI, Doan C, Garcia JC, Zhang N, Prindiville T, Mann S, Trudeau W. Diphenhydramine as an adjunct to sedation for colonoscopy: a double-blind randomized, placebo-controlled study. Gastrointest Endosc 2006; 63: 87-94
10. Bailey PL, Pace NL, Ashburn MA, Moll JW, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 1990; 73:826–830
11. Paspatis GA, Manolaraki M, Xirouchakis G, Papanikolaou N, Chlouverakis G, Gritzali A. Synergistic sedation with midazolam and propofol versus midazolam and pethidine in colonoscopies: a prospective, randomized study. Am J Gastroenterol 2002; 97: 1963–1967
12. Rex DK. The science and politics of propofol. Am J Gastroenterol 2004; 99: 2080-2083
13. Cohen LB, Wecsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol 2006; 101: 967–974
14. Cohen LB, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: A protocol for safe and effective administration by the gastroenterologist. Gastrointest Endosc 2003; 58: 725–732
15. Paspatis GA, Charoniti I, Manolaraki M, Vardas E, Papanikolaou N, Anastasiadou A, Gritzali A. Synergistic sedation with oral midazolam as a premedication and intravenous propofol versus intravenous propofol alone in upper gastrointestinal endoscopies in children: a prospective, randomized study. J Pediatr Gastroenterol Nutr 2006; 43: 195–199
16. Rex DK, Overley C, Walker J. Registered nurse-administrated propofol sedation for upper endoscopy and colonoscopy: Why? When? How? Rev Gastroenterol Disord 2003; 3: 70-80.
17. VanNatta ME, Rex DK. Propofol alone titrated to deep sedation versus propofol in combination with opioids and/or benzodiazepines and titrated to moderate sedation for colonoscopy. Am J Gastroenterol 2006; 101: 2209–2217
18. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Benglinger C. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologists: A prospective observational study of more than 2.000 cases. Gastrointest Endosc 2003; 57: 664-671
19. Kulling D, Rothenbuhler R, Inauen W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. Endoscopy 2003; 35: 679–682
20. D'Honneur G, Rimaniol JM, el Sayed A, Lambert Y, Duvaldestin P. Midazolam/propofol but not propofol alone reversibly depress the swallowing reflex. Acta Anaesthesiol Scand 1994; 38: 244-247
21. Reimann FM, Samson U, Derad I, Fuchs M, Schiefer B, Stange EF. Synergistic sedation with low-dose midazolam and propofol for colonoscopies. Endoscopy 2000; 32: 239-244
22. Lazzaroni M, Bianco- porro G. Premedication, preparation and surveillance (review). Endoscopy 1999; 31: 2-8
23. Short TG, Chiu PG. Propofol and midazolam act synergistically in combination. Br J Anaesth 1992; 67: 539-545
24. Manolaraki MM, Theodoropoulou A, Stroumpos C, Vardas E, Oustamanolakis P, Gritzali A, Chlouverakis G, Paspatis GA. Remifentanil compared with midazolam and pethidine sedation during colonoscopy: a prospective, randomized study. Dig Dis Sci. 2008; 53: 34-40
25. Vargo JJ, Zuccaro G Jr, Dumont JA, Conwell DL, Morrow JB, Shay SS. Automated graphic assessment of respiratory activity is superior to pulse oximetry and visual assessment for the detection of early respiratory depression during therapeutic upper endoscopy. Gastrointest Endosc 2002; 55: 826-831
26. Koch ME, Gevirtz C. Propofol may be safely administered by trained non-anesthesiologists. Con: propofol: far from harmless. Am J Gastroenterol 2004; 99: 1208-1211
27. White PF: Propofol; in White PF (ed): Text-book of Intravenous Anesthesia. Baltimore, Williams & Wilkins, 1997, pp 111-152
28. Bell GD, Charlton JE. Colonoscopy-is sedation necessary and is there any role for intravenous propofol? Endoscopy 2000; 32: 264-267A
29. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Safety of propofol for conscious sedation during endoscopic procedures in high risk patients: A prospective, controlled study. Am J Gastroenterol 2003; 98: 1751-1757
30. Kulling D, Fantin AC, Biro P, Bauerfeind P, Fried M. Safer colonoscopy with patient-controlled analgesia and sedation with propofol and alfentanil. Gastrointest Endosc 2001; 54: 1-7
31. Iber FL, Sutberry M, Gupta R, Kruss D. Evaluation of complications during and after conscious sedation for endoscopy using pulse oximetry. Gastrointest Endosc 1993; 39: 620-625
32. Moerman AT, Foubert LA, Herregods LL, Struys MM, De Wolf DJ, De Looze DA, De Vos MM, Mortier EP. Propofol versus remifentanil for monitored anaesthesia care during colonoscopy. Eur J Anaesthesiol 2003; 20: 461–466
33. Bouvet L, Allaouchiche B, Duflo F, Debon R, Chassard D, Boselli E. Remifentanil is an effective alternative to propofol for patient-controlled analgesia during digestive endoscopic procedures. Can J Anaesth 2004; 51: 122–125
34. Rudner R, Jalowiecki P, Kawecki P, Gonciarz M, Mularczyk A, Petelenz M. Conscious analgesia/sedation with remifentanil and propofol versus total intravenous anesthesia with fentanyl, midazolam, and propofol for outpatient colonoscopy. Gastrointest Endosc 2003 57: 657–663
35. Fechner J, Ihmsen H, Hatterscheid D, Jeleazcov C, Schiessl C, Vornov JJ, Schwilden H, Schóttler J. Comparative pharmacokinetics and pharmacodynamics of the new propofol prodrug GPI 15715 and propofol emulsion. Anesthesiology 2004; 101: 626–39
36. Gibiansky E, Struys MM, Gibiansky L, Vanluchene AL, Vornov J, Mortier EP, Burak E, Van Bortel L. AQUAVAN injection, a water-soluble prodrug of propofol, as a bolus injection: a phase I dose-escalation comparison with DIPRIVAN (part 1): pharmacokinetics. Anesthesiology 2005; 103: 718–29
37. Baron T, Petersen B, Mergener K, Chak A, Cohen J, Deal S,

Hoffman B, Jacobson B, Petrini J, Safdi M, Faigel D Pike I. Quality indicators for endoscopic retrograde cholangiopancreatography. Gastrointest Endosc 2006; 63: S29-S34
38. Jacobson BC, Chak A, Hoffman B, Barron T, Cohen J, Deal S, Mergener K, Petersen B, Petrini J, Safdi M, Faigel DO, Pike I. Quality indicators for endoscopic ultrasonography. Gastrointest Endosc 2006; 63: S35-S38
39. Vargo J, Waing P, Faigel DO, Baron TH, Goldstein JL, Hirota WK, Jacobson BC, Joahnson JF. Guidelines for the use of deep sedation and anesthesia for GI endoscopy. Gastrointest Endosc 2002; 56: 613-617
40. Kyle P. Etzkorn, Fadi Diab, Russell D. Brown, Geetha Dodda, Brian Edelstein, Rudolph Bedford, Rama P. Venu Endoscopic retrograde cholangiopancreatography under general anesthesia: indications and results. Gastrointest Endosc 1998; 47:363-367
41. Wehrmann T, Kokabpick S, Lembcke B, Caspary WF, Seifert H. Efficacy and safety of intra− venous propofol sedation during routine ERCP: a prospective, con− trolled study. Gastrointest Endosc 1999; 49: 677-683
42. Jung M, Hofmann C, Kiesslich R, Brackertz A. Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. Endoscopy 2000; 32: 233-238
43. Riphaus A, Stergiou N, Wehrmann T. Sedation with propofol for routine ERCP in high-risk octogenarians:a randomized controlled study. Am J Gastroenterol 2005; 100: 1957-1963
44. Seifert H, Schmitt TH, Góltekin T, Caspary WF, Wehrmann T. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. Aliment Pharmacol Ther 2000; 14: 1207–1214
45. Paspatis GA, Manolaraki MM, Vardas E, Theodoropoulou A, Chlouverakis G. Deep sedation for endoscopic retrograde cholangiopancreatography: intravenous propofol alone versus intravenous propofol with oral midazolam premedication. Endoscopy. 2008; 40: 308-313
46. Fanti L, Agostoni M, Casati A,Guslandi M, Giollo P,Torri G, Testoni A. Target-controlled propofol infusion during monitored anesthesia in patients undergoing ERCP. Gastrointest Endosc 2004; 60: 361-366
47. Tohda G, Higashi S, Wakahara S, Morikawa M, Sakumoto H, Kane. Propofol sedation during endoscopic procedures: Safe and effective administration by registered nurses supervised by endoscopists. Endoscopy 2006; 38:360-367
48. American society for gastrointestinal endoscopy. Modification in endoscopic practice for the elderly. GI Endoscopy 2000; 52: 849-851
49. Hassall E. NASPGN position paper: requirements for training to ensure competence of endoscopists performing invasive procedures in children. J Pediatr Gastroenterol Nutr 199; 24: 345-347
50. American Academy of Pediatrics, American Academy of Pediatric Dentistry, Cote´ CJ, et al. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006; 118: 2587-2602
51. Fishbein M, Lugo RA, Woddland J, Lininger B, Linscheid T. Evaluation of intranasal midazolam in children undergoing esophago-gastroduodenoscopy. J Pediatr Gastroenterol Nutr 1997;25:261-6
52. Liacouras CA, Mascarenhas M, Poon C, Wenner WJ. Placebo-controlled trial assessing the use of oral midazolam as a premedication to conscious sedation for pediatric endoscopy. Gastrointest Endosc 1998;47: 455-60
53. ASGE STANDARDS OF PRACTICE COMMITTEE, Lee KK, Anderson MA, Baron TH, Banerjee S, Cash BD, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO, Jagannath SB, Lichtenstein D, Shen B, Fanelli RD, Van Guilder T. Modifications in endoscopic practice for pediatric patients. Gastrointest Endosc 2008; 67: 1-9
54. Mamula P, Markowitz JE, Neiswender K, Zimmerman A, Wood S, Garofolo M, Nieberle M, Trautwein A, Lombardi S, Sargent-Harkins L, Lachewitz G, Farace L, Morgan V, Puma A, Cook-Sather SD, Liacouras CA. Safety of intravenous midazolam and fentanyl for pediatric GI endoscopy: prospective study of 1578 endoscopies. Gastrointest Endosc 2007;65:203-10
55. Bahal-O'Mara N, Nahata MC, Murray RD, Linscheid TR, Fishbein M, Heitlinger LA, Li BU, McClung HJ, Potter C, Lininger B. Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. Eur J Clin Pharmacol 1994;47:319-23
56. Chuang E, Wenner WJ, Piccoli DA, Altschuler SM, Liacouras CA. Intravenous sedation in pediatric upper gastrointestinal endoscopy. Gastrointest Endosc 1995;42: 156-60
57. Gilger MA. Conscious sedation for endoscopy in the pediatric patient. Gastroenterol Nurs 1993; 16: 75-79
58. Koh JL, Black DD, Leatherman IK, Harrison RD, Schmitz ML. Experience with an anaesthesiologist interventional model for endoscopy in a pediatric hospital. J Pediatr Gastroenterol Nutr 2001;33:314-8
59. Squires RH, Morriss F, Schluterman S, Drews B, Galyen L, Brown KO. Efficacy, safety, and cost of intravenous sedation versus general anesthesia in children undergoing endoscopic procedures. Gastrointest Endosc 1995;41:99-104