Sedation in Gastrointestinal Endoscopy

Benvenuto Axel, Marcellus Simadibrata**, Dina Ikawari****

*General Practitioner, Abdi Waluyo Hospital, Jakarta
**Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta
***Department of Anesthesiology, Abdi Waluyo Hospital, Jakarta

Corresponding author:
Marcellus Simadibrata. Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-3153957; Facsimile: +62-21-3142454. E-mail: prof.marcellus.s@gmail.com

ABSTRACT

Sedation helps patients to tolerate uncomfortable gastrointestinal endoscopy procedures by relieving anxiety and pain. It also decreases a patient's risk of physical injury during gastrointestinal endoscopy procedures while providing the endoscopist with a good environment for an optimum examination. Not all sedation in gastrointestinal endoscopy is managed by an anesthesiologist. Using sedation has increases risk of cardiopulmonary complications. Therefore, sedation is an important part in gastrointestinal endoscopy to learn. This review will focus on basic pharmacology of sedatives and analgesic, common used drugs in sedation (Propofol, Midazolam, Fentanyl), and their use in gastrointestinal endoscopy.

Keywords: *sedation, endoscopy, analgesia, endoscopic sedation*

ABSTRAK

Sedasi membantu pasien mentoleransi prosedur endoskopi gastrointestinal yang tidak nyaman dengan cara meredakan rasa cemas dan nyeri. Sedasi juga mengurangi risiko terjadi cidera fisik selama prosedur endoskopi gastrointestinal dan memfasilitasi endoskopis agar dapat melakukan pemeriksaan dengan optimal. Tidak semua pemberian obat sedasi pada tindakan endoskopi dikerjakan oleh seorang anestesiologis. Penggunaan obat sedasi memiliki risiko terjadinya gangguan kardiopulmonar. Oleh sebab itu, sedasi merupakan bagian penting untuk dipelajari dalam prosedur endoskopi gastrointestinal. Ulasan ini akan fokus membahas mengenai dasar farmakologi obat hipnotik-sedatif dan analgesia, jenis obat yang umum digunakan (Propofol, Midazolam, Fentanyl) serta penggunaannya pada tindakan endoskopi gastrointestinal.

Kata kunci: *sedasi; endoskopi; analgesia; sedasi endoskopi*

INTRODUCTION

Sedation, which can be defined as a drug-induced depression in the level of consciousness, is an important part in gastrointestinal endoscopy. Sedation helps patients to tolerate uncomfortable procedures by relieving anxiety, discomfort, and pain. It also decreases a patient's risk of physical injury during endoscopic procedures while providing the endoscopist with a good environment for an optimum examination.[1] There are some sedatives and analgesics that can be used to achieve appropriate levels of sedation for gastrointestinal endoscopy.[2]

Although there are benefits from using sedatives and analgesics in gastrointestinal endoscopy procedures,

there are other things that should be considered. Sedation delays patient recovery and discharge. Sedation also increases overall cost, and the risk of cardiopulmonary complications.[1] Sedation is divided into four levels, mild sedation, moderate sedation, deep sedation, and general anesthesia (Table 1).[3] Individuals have different responds to sedatives. Patient may become more deeply sedated than the level that was intended.[1] Therefore, basic pharmacology of sedatives and physiology is necessary to increases the likelihood to achieve targeted level of sedation. Practitioners in endoscopy unit should have the skills necessary to resuscitate or rescue a patient whose level of sedation is deeper than that planned.[3]

The aim of this review is to provide the reader with an overview of the current knowledge of the pharmacology of sedatives and analgesics, common used drugs in sedation (Propofol, Midazolam, Fentanyl), and their use in gastrointestinal endoscopy.

PHARMACOLOGY

Endoscopist should understand the pharmacology, pharmacokinetics (time of onset, peak response, and duration of effect), pharmacodynamics, adverse effect and drugs interactions. The most common used sedatives and analgesics are propofol, benzodiazepine (especially midazolam) and opioid (especially fentanyl).[4]

Propofol

Propofol is a drug that belongs to sedative-hypnotic class. Propofol also has anti-emetic and amnesia effects.[5] Propofol is available for intravenous use. It's available for intravenous administration as an oil-in-water emulsion containing soybean oil, glycerol and egg lecithin. A history of egg allergy doesn't necessarily contraindicate the use of propofol because most egg allergies involve reaction to egg white (albumin), whereas egg lecithin is extracted from egg yolk. Propofol often causes pain at the injection site that can be reduced by prior injection of lidocaine. Propofol can be a good medium for bacterial growth, therefore propofol should be used within 6 hours of the ampoule opening.[6,7]

Propofol works by facilitating γ-aminobutyric acid (GABA), the inhibitory neurotransmitter, especially at $GABA_A$ receptors. Activation of this receptor causes hyperpolarization of the nerve membrane. Propofol also acts on glycine, nicotinic and muscarinic receptors in the spinal cord and brain.[6,8]

Propofol has a rapid onset of action and short recovery time. The depth of sedation increases in a dose-dependent manner. The titration of propofol to the desired level of sedation, not too deep, requires a good clinical assessment of the patients.[5] Propofol is usually combined with opioid and benzodiazepine drugs. The interactions between these drugs create synergistic sedative-hypnotic effects with each other.[9]

Propofol is highly lipophilic, therefore it can quickly cross the blood-brain barrier, which causes rapid onset of action. It also causes the emergence from sedation is quite qrapid due to its fast redistribution to peripheral tissues. Sedation with propofol can be achieved by bolus or continuous infusion. Propofol can make the patient unconscious within 30 seconds. Regardless of the duration of sedation, recovery from the propofol effect occurs within 10-20 minutes after discontinuation of the drug.[5] Propofol also has an anti-emetic effect and less delirium occurrence after recovery than other intravenous sedation drugs. It makes propofol a good sedation drugs for outpatients sedation. Propofol is conjugated in the liver, resulting inactive metabolites that are excreted through urine.[6] Relative dose of propofol does not need adjustment in patients with hepatic or renal impairment.[10,11]

The major side effects of propofol on the cardiovascular system are decreased in arterial blood pressure due to decreased systemic vascular resistance, preload and cardiac contractility. Transient decreases in blood pressure are more prominent in large doses, rapid injections and geriatric patients. Propofol has a profound effect of respiratory depression. This is because propofol inhibits hypoxic ventilation drive and depress the normal respone to hypercarbia. Propofol also decrease cerebral blood flow and intracranial pressure.[6]

Table 1. Definition of general anesthesia and levels of sedation[3]

	Minimal sedation (anxiolysis)	Moderate sedation (conscious sedation)	Deep sedation	General anesthesia
Responsiveness	Normal respone to verbal stimulation	Purposeful respone to verbal or tactile stimulation	Purposeful respone after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	Maybe inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Maintained	Usually maintained	Maybe impaired

Midazolam

Benzodiazepines have multiple pharmacologic effects that help facilitate sedation for endoscopy through interactions with GABA receptors. Similar to propofol, when benzodiazepines bind to $GABA_A$ receptors in the brain, inhibitory action occurs in the central nervous system.[9] Benzodiazepines have anti-anxiety, sedative-hypnotic, anterograde amnesia, anti-convulsions, euphoria, and muscle relaxants effects. The benzodiazepine that is often used for gastrointestinal endoscopy sedation is midazolam. Midazolam has a shorter duration of action, better amnesia effects and superior patient satisfaction than diazepam.[5,12] Midazolam is 1.5 to 3.5 times more potent than diazepam.[5]

Midazolam is a benzodiazepine class, that available in parenteral preparations. Midazolam lipophilic properties results in its rapid distribution across the blood-brain barrier to its site of action in the central nervous system. Midazolam is metabolized in the liver through oxidation and conjugation processes, and its metabolites are excreted through urine.[4] Kidney failure may prolong the duration of sedation in patients receiving midazolam due to its metabolites accumulation (alpha-hydroxymidazolam).[6] Midazolam onset of action occurs within 1 to 2.5 minutes, the peak effect is achieved in 3 to 4 minutes, and the duration of effect is 15 to 80 minutes. The duration of effect of midazolam depends on the duration of its administration. Midazolam excretion decreases in geriatric, obesity patients, and those with hepatic and renal disorders.[4.13,14]

The major side effects of midazolam are respiratory depression, respiratory arrest, and hypotension. The effect of respiratory depression is dose dependent. It's due to the depression of the central ventilator response to hypoxia and hypercapnia. However, paradoxical reactions, include hyperactive and aggressive behaviors have been reported in benzodiazepine. Flumazenil is a specific benzodiazepine-competitive antagonist. Flumazenil is useful for reversing the effects of benzodiazepines. It is the management for overdoses of benzodiazepines. Despite its rapid effect (< 1 min) in restoring the hypnotic-sedative effects, amnesia effects are usually unaffected in the administration of flumazenil. Flumazenil is given intravenously 0.2 mg/min until it reaches the target of consciousness. The dose of flumazenil is usually 0.6 to 1 mg.[4,6]

Fentanyl

Opioid class has strong analgesic effects and little sedative effects. The analgesic effect of opioids comes from binding to opioid receptors (mu, kappa, delta, sigma), that present in the central and peripheral nervous system. It is resulting in inhibition of pain neurotransmission. Opioids can be used orally, rectally, transdermal, subcutaneously, intramuscularly and intravenously. For gastrointestinal endoscopy procedures, it is usually used intravenously. Among others opioid-type drugs, fentanyl is the most widely used for gastrointestinal endoscopy sedation.[9]

Fentanyl is a synthetic opioid. It is lipid-soluble, and 80 to 100 times more potent than morphine. The onset of action for fentanyl is 1 to 2 minutes, the duration of effect is 30 to 60 minutes.[4] Its potency is strong due to its high lipophilic properties, which is also the reason for its rapid penetration to the central nervous system. Elimination of fentanyl is similar to other lipophilic drugs. It is determined by its distribution into adipose tissue.[9] Fentanyl binds to opioid receptors, and inhibits the release of pain neurotransmitters by lowering intracellular Ca^{2+} levels. Fentanyl is commonly used with drugs with sedative-hypnotic effects for sedation in gastrointestinal endoscopy.[5] Fentanyl is metabolized in the liver and excreted through urine.[4] Fentanyl pharmacokinetics are unchanged in patients with renal impairment. Prolonged use results in accumulation of metabolites, but it's inactive and not toxic.[9]

Common side effects of opioids include respiratory depression, nausea, vomiting, constipation, urinary retention, myosis, and myoclonus. Respiratory depression occurs in a dose-dependent manner, and the concomitant use of other sedative-hypnotic drugs with an opioid has a synergistic effect on the risk of respiratory depression. Opioids usually cause only mild hemodynamic disorders.[9] Among other opioids, fentanyl has relative small effect on cardiovascular system.[1] Nausea and vomiting results from stimulation of the chemoreceptor trigger zone in medulla, which occurs in dose-independent manner.[6] Naloxone is an opioid receptor antagonist. It is used to reverse the effects of opioids. The onset of action for naloxone is 1 to 2 minutes and the duration of action is 30 to 45 minutes.[4]

SEDATION IN ACTUAL ENDOSCOPY PRACTICES

Implementation of evidence-based sedatives and analgesics may improve the quality of sedation practice and reduce the incidence of sedation-related adverse events. The combination of experience and basic knowledge is required in the administration of sedatives for safe and effective induction and maintenance. Nowadays, the technique that often used is balanced

anesthesia technique. Balanced anesthesia involves the administration of a mixture of small amounts of several sedatives or analgesics. This technique allows us to reach the desired level of consciousness with minimizing the likelihood of a dose-related adverse reaction from any of the individual drugs. Practical sedation drugs for gastrointestinal endoscopy can be seen in Table 2.[4]

Table 2. Practical sedation regimens for gastrointestinal endoscopy

Drugs	Dose
Midazolam only	Initial dose: 1–2 mg or 0.03 mg/kg Additional dose: 1 mg or 0.02–0.03 mg/kg (every 2-3 mins)
Midazolam + Fentanyl	Initial dose: Midazolam 0.5-1 mg + Fentanyl 12.5-75 µg Additional dose: Midazolam 1 mg or Fentanyl 12.5-50 µg (every 1-3 mins)
Propofol only Bolus	Initial dose: 10-60 mg Additional dose: 10-20 mg (every 30 secs) Continuous infusion: 2-5 mg/kg/hr or 100-200 mg/hr, with or without initial bolus 0.25-0.5 mg/kg
Continuous	Initial dose: Midazolam 0.5-2.5 mg + Propofol 10-40 mg or up to 0.5 mg/kg Additional dose: Propofol 5-20 mg (severy 30 secs)
Propofol + Midazolam	Initial dose: Fentanyl 25-75 µg + Propofol 10-40 mg or up to 0.5 mg/kg
Propofol + Fentanyl	Additional dose: Propofol 5-20 mg (every 30 secs)

Zhang et al performed a meta-analysis about the comparisson of propofol and midazolam for sedation in gastrointestinal endoscopy. Data show propofol has higher incidence of hypotension than midazolam. However, propofol has higher satisfaction score than midazolam according to endoscopists. There was no significant difference in satisfaction score according to patient.[15]

Midazolam is the most widely used benzodiazepine for gastrointestinal endoscopy sedation due to its rapid onset of action and short recovery time compared to other benzodiazepines.[4,16] Barriga et al evaluated the use of midazolam alone compared to midazolam combined with fentanyl for gastrointestinal endoscopy sedation. From the endoscopist point of view, patients in the combination group had better tolerance than midazolam alone group. There was no significant difference in duration of action and side effects between two groups.[17]

According to Singh et al, the use of single dose 50 µg fentanyl combined with propofol reduces the need of propofol in sedation practice, without affecting the recovery time.[18] The research of Yoon et al compared the use of propofol alone and propofol combined with other sedatives or analgesics in gastrointestinal endoscopy. There was no significant difference in the incidence of sedation-related adverse (respiratory distress, hypotension, arrhythmia), recovery time, duration of action, endoscopist and patient satisfaction between both groups. However, the average dose of propofol used was higher in propofol alone group.[19]

CONCLUSION

Various sedatives drugs are used to facilitate sedation in gastrointestinal endoscopy, either used as a single agent or combined. It is important for endoscopists to understand the basic pharmacology of hypnotic-sedative drugs and analgesics that used in sedation practices, because not all sedation in gastrointestinal endoscopy is managed by an anesthesiologist. The combination of experience and basic knowledge is required to optimize the use of sedatives drugs in gastrointestinal endoscopy and decrease the incident of sedation-related adverse event.

REFERENCES

1. Cohen LB, Delegge MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, et al. AGA Institute Review of Endoscopic Sedation. Gastroenterology 2007;133:675-701
2. Early DS, Vargo JJ, Chandrasekhara V, Fisher DA, Khashab MA, Saltzman JR. Guidelines for sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2018;87:327-37.
3. Gross JB, Bailey PL, Connis RT, Cote CJ, Davis FG, Epstein BS, et al. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004–17.
4. Moon SH. Sedation regimens for gastrointestinal endoscopy. Clin Endosc 2014;47:135-40.
5. Triantafillidis JK, Merikas E, Nikolakis D, Papalois A. Sedation in gastrointestinal endoscopy: current issues. World J Gastroenterol 2013;19:463-81.
6. Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's Clinical Anesthesiology. 5th Ed. New York: McGraw-Hill Education 2013
7. Muller AE, Huisman I, Roos PJ, Rietveld AP, Klein J, Harbers JBM, et al. Outbreak of severe sepsis due to contaminated propofol: lessons to learn. J Hosp Infect 2010;76:225-30.
8. Trapani G, Altomare C, Sanna E, Biggio G, Liso G. Propofol in Anesthesia. Mechanism of action, structure-activity, relationships, and drug delivery. Curr Med Chem 2000;7:249-71.
9. Horn E, Nesbit SA. Pharmacology and pharmacokinetics of sedatives and analgesics. Gastrointest Endosc Clin N Am 2004;14:247-68.
10. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding propofol in patient with cirrhosis. Anesthesiology 1988;69:887-91.
11. Ickx B, Cockshott ID, Byttebier L, De Pauw L, Vandesteene A, D'Hollander AA. Propofol infusion for induction and

maintenance of anaesthesia in patients with end-stage renal disease. Br J Anaesth 1998;81:854–60.

12. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc 2008; 67:910-23.
13. Pentikainen PJ, Valisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of Midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29:272-77.
14. Vinik HR, Reves JG, Greenblatt DJ, Abernethy DR, Smith LR. The pharmacokinetics of Midazolam in chronic renal failure patients. Anesthesiology 1983;59:390-94.
15. Zhang R, Lu Q, Wu Y. The comparison of Midazolam and propofol in gastrointestinal endoscopy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech 2018
16. Lichtenstein DR, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2008;68:815-26.
17. Barriga J, Sachdev MS, Royall L, Brown G, Tombazzi CR. Sedation for upper endoscopy: comparison of Midazolam versus Fentanyl plus Midazolam. South Med J 2008;101:362-66.
18. Singh SA, Prakash K, Sharma S, Dhakate G, Bhatia V. Comparison of propofol alone and in combination with ketamine or fentanyl for sedation in endoscopic ultrasonography. Korean J Anesthesiol 2018;71:43-7.
19. Yoon SW, Choi GJ, Lee OH, Yoon IJ, Kang H, Baek CW, et al. Comparison of propofol monotherapy and propofol combination therapy for sedation during gastrointestinal endoscopy: a systematic review and meta-analysis. Dig Endosc 2018