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EDITORIAL

Sedative and Analgesic Drugs for Gastrointestinal Endoscopic Procedure

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ABSTRACT

Gastrointestinal endoscopy has become an essential modality for evaluation and treatment of gastrointestinal tract abnormalities. This procedure is complex and may be unsafe if special concerns are not considered. The goal of procedural sedation in endoscopic procedure is the safe and effective control of pain and anxiety, to provide an appropriate degree of memory loss or decreased awareness and to improve endoscopic performance especially in therapeutic procedures. Regardless of regimen used, the safe administration of sedative and analgesic drugs requires an awareness of the particular needs of the patients. The most commonly used sedation regimen for sedation in gastrointestinal endoscopic procedure is still the combination of benzodiazepines and opioids. In addition, the use of propofol has increased enormously in the past decade. New sedative agents are currently used and studied. Although sedation in this endoscopic procedure is considered safe, the sedation has a potential for complications. Sedation-related complications can more easily occur even in healthy populations. Risk evaluation before the procedure and monitoring during and after the procedure as well as increased awareness of the sedation-related complications must be performed. Furthermore, properly trained staff and emergency equipment should be available. This article reviews pharmacokinetics and pharmacodynamics of sedative and analgesic drugs and discusses the clinical use in gastrointestinal endoscopic procedure.

Key words: Sedative; Analgesic; Gastrointestinal endoscopy

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INTRODUCTION

Medications used in intravenous procedural sedation should be understood at a pharmacologic level. Conscious sedation, or moderate sedation, is used for procedures that are typically not well tolerated, but that also do not require deep or prolonged sedation. Patients should be kept at a level where they can respond to verbal commands, and should respond purposefully when stimulated. Titration of doses should be done cautiously, and patients should be monitored for effectiveness, adverse effects, altered metabolism, and potential drug interactions.

Sedation always has been a critical component of performing gastrointestinal endoscopy (GIE) procedures. The aim of sedation for these procedures is to increase patient's comfort, to improve endoscopic performance and to increase patient and endoscopist satisfaction. The need for sedation is decided by the type of endoscopy, duration of procedure, degree of endoscopic difficulty, patient physical status and physicians' preferences. The sedation regimen for GIE procedures is still varied. Safe sedation of patients for diagnostic or therapeutic procedures requires a combination of properly trained physicians and suitable facilities. Additionally, appropriate selection and preparation of patients, suitable sedative technique, application of drugs, adequate monitoring, and proper recovery of patients is essential. Sedation practices for GIE procedures vary widely. The majority of GIE patients are ambulatory cases. Most of this procedure requires a short time. So, short acting, rapid onset drugs with little adverse effects and improved safety profiles are commonly used[1].

Pharmacokinetics of a drug is highly dependent on dosage, route of administration, pharmaceutical preparation, and drug-related factors. Patient-specific factors including concomitant pharmacotherapy, comorbidities, and patient characteristics may also alter pharmacokinetic parameters. Pharmacodynamics focus on the effects that the drug has on the body. This includes the mechanism

of action as well as the time course and character of a drug's effect at the recepto r site. This chapter will provide an overview of the pharmacology of these sedative and analgesic drugs for GIE procedures. Pharmacology of commonly used sedative and analgesic agents will be discussed. The mechanisms of action, adverse effects, pharmacologic considerations, and cardiopulmonary effects are described. This present review focuses on commonly used sedative and analgesic drugs in GIE sedation.

Properties of an ideal intravenous anesthetic agent are chemically stable, water soluble, long shelf-life, bacteriostatic, painless on injection, thrombophlebitis rare, harmless if injected intra-arterially or extravasated, low incidence of adverse effects, compatible with other fluids and drugs, rapid induction of anesthesia, good antiemetic, analgesic and anticonvulsant, predictable recovery and short duration of action, inert metabolites, can be infused long term, no teratogenesis and no emergence reaction or hangover effect as well as no cardiorespiratory depression[2].

OPIOIDS

Opioids are commonly used as analgesic agents in anesthesia and pain management. Opiates are directly derived from the opium poppy, and the term "opioid" refers to both natural and synthetic drugs that act on opioid receptors systemically[3]. When choosing an opioid agent for procedural sedation, individual drug pharmacokinetic, pharmacodynamic, and adverse effect profiles should be considered. Ideal opioids for use in procedural sedation would have rapid onset, analgesic effects, minimal or no respiratory depression, minimal effects on hemodynamics, and low incidence of adverse effects.

Mechanism of action

Opioids and their derivatives have direct agonist action on m-opioid, k-opioid, and δ-opioid receptors. This produces analgesia and sedation without amnesia. Opioid receptors are located on both peripheral and central nerves, as well as the gastrointestinal tract[3]. The settings of the opioid receptors systemically lead to both desired analgesia, as well as common adverse effects seen with these agents. Multiple m-receptor subtypes have been identified, but m-1 and m-2 exhibit greater affinity for opioid ligands. The m-1 receptors produce analgesic and euphoric effects, whereas m-2 receptor activity results in respiratory depression, sedation, and pruritus. Variations in m-receptor subtype expression may account for the variability seen in opioid response between patients[4]. The k-receptors are located in the limbic system, brain stem, and spinal cord. Activation of k-opioid receptors results in spinal analgesia, sedation, and respiratory depression.

When opioid receptors located on peripheral nociceptive fibers are agonized, direct inhibition of voltage-dependent calcium channel results. This leads to decreased cyclic adenosine monophosphate levels, which blocks the release of pain neurotransmitters including glutamate, substance P and calcitonin. Opioid agonist also results in activation of presynaptic receptors of gamma-amino butyric acid (GABA) receptors, which increases dopaminergic activity and results in euphoric effects[3].

Adverse effects

Opioids exhibit a variety of untoward effects, some of which may be dose-limiting when used for procedural sedation. Central nervous system depression and respiratory depression are the two effects that occur acutely with increased doses[5]. The m-receptor activity in gastrointestinal tract can cause slowed gastrointestinal motility, constipation, and ileus with prolonged use. Nausea and vomiting may also occur. Hypotension and bradycardia also result from decreased sympathetic function and histamine release.

FENTANYL

Fentanyl is a potent synthetic opioid with no intrinsic anxiolytic or amnestic properties. It has a rapid onset, short duration of action, lack of direct of myocardial depressant effects, and absence of histamine release, making it ideal agent for use GIE sedation. Intravenous fentanyl can be easily and rapidly titrated for painful procedures. The combination of fentanyl and midazolam is a popular regimen, with a safety profile when both drugs are carefully titrated[6-8]. Similar to all opioids, fentanyl can cause respiratory depression including apnea and nausea and vomiting. It can also produce the decrease of heart rate and skeletal muscle rigidity.

Pharmacologic considerations

Fentanyl and its derivatives are more lipophilic compared with other opioids used in procedural sedation, facilitating rapid distribution into the central nervous system. The onset of action is 30-60 sec, peak effect is about 5-15 min, and duration of action is 30-45 min. Its dose for GIE procedure is 1-2 mcg/kg, with a maximum dose of 100-150 mcg in most adult patients.

Cardiorespiratory effects

Fentanyl does not have as significant of an effect on hemodynamic relative to morphine and meperidine. This may be due to decreased histamine release, leading to decreased incidence of hypotension. However, respiratory depression is similar to other opioid agents. Fentanyl and its analogs have rapid elimination half-lives, so the time to reversal of respiratory depression and sedation is increased[3].

MEPERIDINE

Meperidine (pethidine) is a less potent phenylpiperidine synthetic opioid. It has fallen out of favor for use both as an analgesic agent and for procedural sedation secondary to its safety profile and increased familiarity with more ideal agents such as fentanyl. Its onset of action is 1-3 min, peak effect is 5-20 min, and duration of action is about 2-4 hour. Intravenous dose of meperidine in adult patients is 0.5-2 mg/kg with a maximum dose of 100 mg. The metabolites of meperidine are toxic to the central nervous system at high doses and in the patients with renal impairment. Fatal reactions have also occurred in patients taking monoamine oxidase inhibitors (MAOI) or in patients with hyperthyroidism[9]. Meperidine 0.5-1.0 mg/kg IV combined with midazolam 0.05-0.1 mg/kg IV provides effective sedation for GIE procedure. However, meperidine is not recommended for procedural sedation in the emergency department.

Pharmacologic considerations

Meperidine requires much higher doses relative to other opioid agents to exhibit similar effects secondary to decreased potency. It has a similar onset of action and shorter half-life relative to morphine, about 10-15 min and 3-4 hour, respectively. Meperidine is metabolized hepatically through demethylation to form normeperidine. Normeperidine is an active metabolite that is cleared renally. At high concentrations, normeperidine leads to neurotoxicity in the form of seizures and myoclonus. Prolonged accumulation can cause renal toxicity and decreased renal function. Fatal reactions have also occurred in patients taking MAOI or in patients with hyperthyroidism[9]. It should not be administered to patients who use MAOI.

Cardiorespiratory effects

Meperidine has similar effects on blood pressure relative to morphine and may induce orthostatic hypotension. Meperidine may lead to tachycardia, as opposed to bradycardia that may be caused by morphine and its derivatives. It also causes respiratory depression, similar to other opioid agents used for procedural sedation.

REMIFENTANIL

Remifentanil is the most recently introduced opioid. It is a fentanyl analog with a methyl ester group that permits the molecule to be hydrolyzed by plasma and tissue esterases. Remifentanil has a high metabolic clearance. Its metabolism is not affected by genetics, age, hepatic failure and renal failure. The context sensitive half-life is about 3-5 min regardless of duration of dosing. Therefore, it makes an ideal drug for intravenous sedation. Its action is of rapid onset and ending, and the drug can be easily controlled in order to obtain the anesthetic level. However, postoperative analgesia must be planned because the end of analgesic action is practically immediate[10]. Remifentanil has high lipid solubility and relatively high unbound unionized fraction at physiologic pH result in peak effect compartment concentration within 1-2 min after bolus administration.

The prescribing information suggests a loading dose of up to 1 mcg/kg and a maintenance infusion of 0.05-2 mcg/kg/min. Elderly patients require less remifentanil because of altered pharmacokinetics and pharmacodynamics that involve a substantial reduction in central compartment volume and clearance[11]. Dosing of remifentanil should be adjusted to lean body mass and that elderly patients require as much as 50%-70% dosage reduction. When using remifentanil as opioid component of anesthesia, precautions have to be taken to ensure analgesia that is appropriate to the degree of anticipated postoperative pain before discontinuing the remifentanil infusion. This is often accomplished with a combination of nonopioid analgesics given well in advance of remifentanil discontinuation, often at or before induction or toward the completion of surgery.

Remifentanil can provide intraoperative hemodynamic stability for the patient without the risk that the drug accumulates and prolongs postoperative recovery. However, remifentanil contributes to the typical opioid-related side effects of bradycardia and potential to produce chest wall rigidity and nausea/vomiting. Bolus doses of remifentanil for postoperative analgesia are generally not recommended because of the association with an increased risk of respiratory depression and apnea. Target controlled infusion of remifentanil is another alternative after anesthesia using remifentanil.

Several studies show that post-operative pain occurs faster after anesthesia using remifentanil than after anesthesia using other opioids. Postoperative pain management must be started at least 20 min before discontinuing remifentanil infusion. Administration of a longer-acting opioid during short procedures provides successful pain management and does not prolong hospital stay for outpatients. Longer-acting opioids are required to ensure a satisfactory transition from remifentanil to adequate postoperative analgesia. Patient who is breathing spontaneously in the immediate post-operative period requires close monitoring and supervision to ensure individual titration of the analgesic versus the respiratory depressant effect.

Clinical uses

The role of remifentanil for sedation in GIE procedure is not entirely established. Combined use of opioids and benzodiazepines often results in delayed discharge after GIE procedure. For this reason, remifentanil may be well suited for sedation during this procedure. Intravenous remifentanil and propofol were more efficient for gastroscopy than IV fentanyl and propofol[12]. Remifentanil patient controlled analgesia (PCA) is also a safe approach to sedation for colonoscopy[13]. The study of Fanti and colleges showed that IV remifentanil PCA provided the same quality of sedoanalgesia during colonoscopy as the sedation protocol with IV bolus meperidine. In addition, the patients' overall satisfaction with the quality of this sedation protocol was similar. No serious adverse effect was reported[14]. Remifentanil infusions and meperidine boluses are equally well tolerated in older patients undergoing ambulatory colonoscopy when administered by an anesthesia provider[15]. Patient controlled sedation with propofol and remifentanil is a suitable and well-accepted sedation method for ERCP procedure[16].

NALOXONE

Opioid reversal may become necessary in the case of respiratory depression or other toxicities. Naloxone is a pure opioid antagonist that competes with and displaces opioid molecules at the receptor site. It is active on peripheral and central opioid receptors. Naloxone may be administered through intravenous, intramuscular, or subcutaneous routes in doses of 0.04-0.4 mg, with repeated dosing until reversal of opioid intoxication. However, the analgesic effect of the opioids will also be reversed with naloxone use and withdrawal is possible. Dosing may need to be repeated, especially with longer acting opioids or those that have active metabolites[17]. In certain cases, continuous infusion of naloxone may be considered at a dose of 4-8 mcg/kg/h. Liver is responsible for metabolizing naloxone through glucuronidation to its primary metabolite, naloxone-3-glucuronide. The duration of action of naloxone is about 30-45 min.

Rapid administration of naloxone can increase sympathetic activation. This can commonly result in nausea, vomiting, hypertension, and tachycardia. In rare cases, arrhythmias and pulmonary edema may also be noted. Slow titration and dose to effect should be utilized in effort to reduce the likelihood of these adverse effects. Repeat doses to avoid opioid intoxication may be necessary due to the short duration of action of naloxone[17]. It is best to define an observation period of 1-2 h after administering naloxone to monitor for renarcotization as well as any adverse effects. Smaller doses may be appropriate in the elderly patients since naloxone induces secretion of catecholamines and may create cardiovascular instability[18]. The duration of treatment depends on the half-life of the opioid being reversed. Similarly to flumazenil, naloxone can cause acute withdrawal syndrome including pain, hypertension, tachycardia and pulmonary edema.

Although the routine usage of naloxone is not recommended, it should be available for uses in emergency situations. Naloxone administration should always be combined with additional supportive treatments including supplemental oxygen, fluid resuscitation, and frequent assessment of the patient's condition is mandatory for continuously evaluating the resuscitating efforts. Importantly, the extended observation of patients is the need after administration of naloxone as recurrence of central nervous system depression may be observed when the antagonistic effects have ceased.

BENZODIAZEPINES

Benzodiazepines are the most commonly used agents for preoperative anxiolysis as adjuncts to induction and sedation. They are lipid soluble and protein bound. Redistribution is the major determinant of the onset and duration of effect after a single intravenous dose. Benzodiazepines are potent anxiolytics, produce anterograde amnesia and have a favorable therapeutic index. Consequently, they reduce induction dose requirements by several mechanisms

including pharmacodynamic interactions with hypnotics. They have anticonvulsant activity and are used in the acute management of status epilepticus. Benzodiazepines generally have no analgesic properties, but they potentiate the effects of both sedatives and analgesics. They depress respiration and the responses to hypoxia and carbon dioxide but less so than other induction agents, and have minimal cardiovascular depressant effects.

Benzodiazepines are commonly used for procedural sedation. Specially, the survey indicated that up to 75% of physicians utilized benzodiazepines and narcotics for sedation during GIE procedures[19]. Benzodiazepines have many pharmacodynamic characteristics that make them ideal medications for conscious sedation including an anxiolytic effect, anterograde amnesia and sedation. Other effects include hypnosis, muscle relaxation, and anticonvulsant activity. In most GIE cases they are administered by the intravenous route.

Benzodiazepines-related adverse effects include respiratory depression, impaired airway reflexes and cardiovascular depression as well as impaired consciousness and coma. They should be avoided or used with caution in the elderly and in severe co-morbidities patients. Patients with impaired consciousness are also very sensitive to sedative and analgesic drugs. Interactions with ethanol may be serious. The effects of benzodiazepines can be reversed with the specific antagonist flumazenil. In chronic use they may lead to abuse and co-dependence. The long-term use of benzodiazepines must be considered with caution because there may be withdrawal symptoms.

Mechanism of action

Benzodiazepines exert their effects by enhancing gamma-amino-butyric acid (GABA) activity. GABA is the main inhibitory neurotransmitter of the central nervous system. The mechanism of action of benzodiazepines may be due to potentiation of the neural inhibition mediated by GABA, increasing chloride conductance via the GABA channel. The binding of the benzodiazepines to the GABA receptor is of high affinity, saturable and stereospecific. The GABA receptor is composed of 5 subunits forming a chloride channel. When GABA binds to the receptor, a conformation change occurs, allowing chloride ions to flow into the neuron hyperpolarizing the cell and reducing the likelihood of an action potential being generated. Differing pharmacologic effects can be seen depending on GABA subunit pharmacology.

Adverse effects

Agonist of GABA receptor can cause respiratory depression, apnea, and decrease muscle tone in the upper airway. This risk for respiratory depression and over-sedation increases with high or repeated doses. Therefore when utilized for conscious sedation, doses need to be carefully titrated to avoid oversedation and respiratory depression. Low doses should be started initially and titrated to response especially in the elderly patients.

Benzodiazepines are metabolized through the cytochrome P-450 system, thus patients with hepatic insufficiency or patients taking cytochrome P-450 inhibitors will have a prolonged half-life and duration of effect. As benzodiazepines can cause respiratory depression, they should be used with caution in patients with respiratory conditions such as chronic obstructive pulmonary disease or obstructive sleep apnea. In addition, benzodiazepines should be used cautiously in elderly patients as they typically have prolonged duration of effect. The increased half life in elderly patients could be due to reductions in hepatic blood flow, reduced enzyme activity, and renal insufficiency. Patients who abuse alcohol may require higher doses of benzodiazepines to obtain the desired effect due to changes at the GABA receptor site[20].

For procedural sedation it is typically the pharmacokinetic differences that dictate which benzodiazepine to utilize. The onset and duration of effect after the administration of a single dose of a benzodiazepine is related to each respective agent's lipid solubility. Benzodiazepines with greater lipid solubility will have more rapid onsets because they will cross through the blood-brain barrier into the central nervous system more rapidly. The duration of action will be shorter as the volume of distribution increases because the drug will distribute out of the serum and into the periphery, which will then cause redistribution of the benzodiazepines out of central nervous system[21].

MIDAZOLAM

Pharmacologic considerations

Midazolam is water soluble, and displays pH-dependent opening of the benzodiazepine ring below a pH of about 4.0. It is the most common benzodiazepine used for conscious sedation. One advantage over diazepam and is that midazolam is water-soluble and can be administered intramuscularly or intravenous with less risk of extravasation. Diazepam is dissolved in a propylene glycol base, whereas midazolam is stable in dextrose or normal saline. This is beneficial as propylene glycol can lead to a hyperosmolar metabolic acidosis when administered as a continuous infusion at high doses. At physiological pH, midazolam is converted into a more lipid-soluble form and thus has a very rapid onset of action and a short duration of action.

Midazolam has the shortest half-life and duration of action when compared with diazepam, making it an ideal agent when prolonged sedation is not required. The active metabolite of midazolam (1-hydroxy-midazolam) is renally eliminated and therefore the half-life may be prolonged in patients with renal insufficiency. In addition, the concurrent administration of cytochrome P-450 inhibitors such as protease inhibitors and calcium channel blockers may inhibit the metabolism of midazolam and therefore prolong the duration of action as well.

Cardiorespiratory effects

Midazolam can cause hypotension at higher doses and is more common in patients also receiving opioids and in pediatric patients. It is thought to cause hypotension through peripheral vasodilation, which can be more pronounced in hypovolemic patients. It can cause respiratory arrest or apnea. The combination of midazolam and fentanyl may increase the risk of respiratory depression. In addition, rapid administration can increase the risk for apnea, especially when an opioid is administered before midazolam.

Clinical uses

Midazolam is an ideal agent to provide anxiolysis and anterograde amnesia for short procedures. Many of the cardiopulmonary side effects can be increased when administered with an opioid, but co-administration occurs often as midazolam does not have analgesic affects. Therefore, careful titration should be used as these combinations are utilized for procedural sedation. In addition, midazolam should also be titrated carefully in patients at risks such as elderly, hepatic insufficiency and renal insufficiency. Generally, midazolam can rarely cause paradoxical reactions such as hyperactivity or aggressive behavior. This reaction is more common in children and psychiatric patients and, if necessary, can be reversed with flumazenil.

DIAZEPAM

Pharmacologic considerations

The use of diazepam for procedural sedation has been replaced by midazolam. Compared with midazolam, diazepam has significantly longer duration of action and is less water soluble. Diazepam can cause significant pain when administered intramuscularly or intravenously, thrombophlebitis, and extravasation. It is also very lipophilic at physiological pH and therefore has a very rapid onset of action. However, it has a longer duration of action primarily because it is metabolized to active metabolites with very long half-lives as well. In addition, the duration of action will be increased in patients taking cytochrome P-450 inhibitors, elderly, and patients with hepatic dysfunction.

Cardiorespiratory effects

Diazepam may also cause hypotension and vasodilation but is less likely to cause hypotension when compared with midazolam. Rapid administration can cause hypotension and bradycardia due to the diluent propylene glycol. Just as with midazolam, the combination of opioids and diazepam will increase the risk for hypotension and respiratory depression. Death resulting from diazepam alone is extremely rare. Most deaths are secondary to a combination of alcohol or other sedative and hypnotic agents[22].

Clinical uses

The use of diazepam for sedation in GIE procedures is limited due to the long half-life, and thus has been replaced by midazolam.

FLUMAZENIL

Flumazenil is the reversal agent for benzodiazepines. It selectively binds to the GABAA receptor complex, prevents the attachment of benzodiazepines to their receptor, and inhibits or reverses their effects on the central nervous system[23]. However, flumazenil will not reverse other GABA agonists, such as barbiturates. Although it is beneficial to have antidote available, the routine use of flumazenil should be avoided by careful titration of benzodiazepines given during conscious (moderate) sedation. Flumazenil administration can result in seizures, especially in patients on chronic benzodiazepines or patients who recently received repeated doses.

The onset of flumazenil is typically within 3 min and duration of action lasting approximately 1 h. Patients should be monitored for resedation as the effects of flumazenil may wear off before the benzodiazepines are originally administered, depending on the half-life. The initial dose is 0.2 mg over 15 sec. This can be repeated up to 4 times every minute until the desired level of consciousness is obtained. If resedation is noted, repeat doses can be administered every 20 min. The maximum dose of flumazenil is 1 mg/dose and 3 mg/h. Because the duration of the sedative effect of midazolam may reach 80 min, there is always a possibility for resedation of the patient. Similar to naloxone, flumazenil can cause acute withdrawal syndrome including seizures in the patients who receive benzodiazepines chronically[24].

Routine usage of flumazenil for the reversal of benzodiazepine-induced sedation is discouraged by recent guidelines[25]. Benzodiazepines are commonly used for sedation for GIE procedures in the endoscopy units. In addition, flumazenil is should be available for the use in emergency situations in particular when respiratory depression becomes life-threatening, the patient becomes apneic or hypoxemic and when tracheal intubation and mask ventilation is being considered.

PROPOFOL

Propofol is a phenol derivative with sedative, hypnotic and anesthetic properties. It has antiemetic, anxiolytic, hypnotic, amnestic and anesthetic properties, but it does not have analgesic effects[2]. Propofol is presented as a white oil-in-water emulsion containing 1% or more recently 2% propofol in soy a bean oil, egg phosphatid and glycerol. The solution has a pH of around 7.0 and is stable at room temperature. Propofol is 98% protein bound and undergoes hepatic metabolism to glucuronide metabolites, which are ultimately excreted in urine. This drug is arguably the most frequently used intravenous induction agent in the western countries. However, propofol is legally used by anesthesiologists and anesthetic personnel in many countries including Thailand.

The disadvantage of propofol is its narrow therapeutic range and risk of inadvertent general anesthesia and that is the reason why it should be routinely administered by anesthesiologists. Propofol does not significantly accumulate after repeated boluses, so it is especially suitable for long term infusions during surgery as part of a total intravenous anesthesia technique. Today, physicians feel that propofol is the agent of choice for sedation for GIE procedures[26,27]. Propofol guarantees an excellent level of procedural success, optimal timing and maximal patient comfort. Increasing demand for sedating and properly monitoring patients may not be met by anesthesiology departments. Currently, the use of propofol in this setting by non-anesthesiologists is controversial[28,29]. Propofol-based sedation is safe and highly effective. Mild respiratory adverse events occur frequently and major complications may happen rarely, but adverse events do not occur more frequently compared to other sedation regimens[7,30,31].

Pharmacologic considerations

The mechanism of action of propofol is not completely understood, but is thought to cause central nervous system depression as a postsynaptic GABAA agonist and also induces presynaptic release of GABA. Propofol is also an antagonist at N-methyl-D-aspartate receptors[32]. The onset of action is rapid (9-50 sec) as there is rapid equilibration between the plasma and brain after an IV bolus. Likewise, discontinuation of propofol after maintenance of anesthesia results in rapid awakening. It has an initial half-life of 40 min and terminal half-life of 4-7 h. The pharmacokinetic profile of propofol makes it extremely useful for anesthesia and sedation. It is eliminated through hepatic conjugation to inactive metabolites. Propofol has a volume distribution of 2-10 L/kg initially but approaches 60 L/kg after a 10-day infusion. Elderly patients achieve a higher peak concentration; therefore, a lower dose of propofol should be utilized to avoid adverse effects[33].

Cardiorespiratory effects

Propofol causes a significant reduction in arterial blood pressure by decreasing systemic vascular resistance, preload and myocardial contractility. These effects are more prominent in patients with compromised cardiac function and the elderly patients. Following an induction dose, propofol causes apnea, inhibits hypoxic ventilatory drive and impairs the response to hypercarbia. Induction of anesthesia with propofol is frequently associated with upper airway obstruction and apnea. Hypotension, oxygen desaturation, apnea, and airway obstruction are more prominent after a rapid bolus. Induction at a slow rate can prevent some undesirable side effects such as hemodynamic instability and apnea. Patients should be continuously monitored for these possible adverse effects. Consequently, patients may experience burning and pain during propofol administration. This experience can

be prevented by using larger veins of forearm or antecubital fossa or administering lidocaine before injection. Short-term use of propofol is associated with a myoclonic syndrome manifesting as opisthotonus, myoclonus and myoclonic seizure like activity[34].

The use of propofol has been associated with a syndrome of metabolic derangements and organ system failures known as propofol-related infusion syndrome. Propofol-infusion syndrome is characterized by refractory bradycardia leading to asystole in the presence of one or more of the following: metabolic acidosis, hyperkalemia, rhabdomyolysis, hepatomegaly, acute kidney injury, and hyperlipidemia. It is most common in patients receiving high-dose infusions for more than 48 h at rates of 4-5 mg/kg/h or greater. However, this syndrome has been reported after large-dose, short-term infusions during anesthesia[35]. Predisposing factors to the development of propofol-infusion syndrome include young age, severe brain injury, respiratory compromise, concurrent exogenous administration of catecholamines or glucocorticoids, undiagnosed mitochondrial myopathy, and inadequate carbohydrate intake.

Clinical use

The use of propofol for sedation is recommended only for persons with appropriate training in administration of general anesthesia and not involved in the conduction of diagnostic or therapeutic procedure[36]. Generally, propofol is used for induction and maintenance of anesthesia as well as sedation in mechanically ventilated intensive care patients. It is not recommended for use in obstetrics or in nursing mothers. Its quick onset and short duration of action are ideal for when rapid awakening is desired. Rapid bolus administrations should be avoided to prevent adverse effects such as hypotension and respiratory depression or apnea. In addition, the sedation-related hypotension rate was significantly low when propofol was used in the diluted form[37]. Initial intravenous bolus dose of propofol is 1.0 mg/kg and is followed by 0.5 mg/kg, and the repeated dose is needed. Continuous intravenous infusion of propofol dose is 100-150 mcg/kg/min.

Propofol administration techniques

Many methods for propofol delivery have been used for sedation for GIE procedures. Generally, propofol is administered intravenously as a repeated bolus injection, continuous infusion or a mixture of both. In the bolus technique, the initial bolus dose is adjusted according to the patient's weight, age, ASA physical status and comorbidities. Continuous propofol infusion is titrated to the desired sedation level and to the patient's characteristics[1].

Other administration techniques of propofol delivery such as target controlled infusion (TCI), patient controlled sedation (PCS) or computer assisted personalized sedation (CAPS) have been investigated. Propofol TCI rather than bolus method may be a better choice for the prevention of hemodynamic response during GIE procedure. However, propofol TCI does not confer any benefit over bolus propofol with respect to drug consumption and recovery profile for sedation in colonoscopic procedure[38]. PCS with propofol is effective and results in high patient satisfaction and faster discharge[39]. Moreover, PCS has been demonstrated to be the effective technique for pain control during GIE procedure[40]. CAPS uses feedback from the real time measures of drug effect and patient reaction to tactile stimuli to control propofol infusion[41].

Anesthesiologist-administered propofol

Generally, propofol is administered by anesthesiologists for sedation/anesthesia in various surgical procedures including GIE procedures. To date, there are several controversial issues about propofol administration. For example, who, when and how should administer propofol? In Western countries, propofol can be performed by well-trained registered nurses or physicians. So, anesthesiologist-administered propofol compared with nonanesthesiologist-administered propofol is less cost-effectiveness. However, in developing countries like Thailand, propofol-based sedation is performed by anesthesiologists or anesthetic nurses and is usually done in the operating room. In Thailand, topical anesthesia is the most common anesthetic technique used for GIE procedure. General anesthesia for this procedure is performed about 3-5%[42].

Cost-effectiveness of the anesthesiologist assistance for colorectal cancer screening is controversial. The absolute economic benefit of endoscopist-directed administration of propofol (EDP) implementation in a screening setting is probably substantial. The impact of an eventual EDP-related mortality on EDP cost-effectiveness appears marginal. The huge economic and medical resources entailed by anesthetist-assisted colonoscopy could be more efficiently invested in other clinical fields[43]. Several studies confirmed that anesthesiologist-administered sedation for ERCP patients is safe and effective. Cardiac and respiratory events are generally minor. The procedure interruption or premature termination is rare in the setting of anesthesiologist-administered sedation[44]. However, no randomized, controlled studies comparing anesthesiologist-administered propofol with nonanesthesiologist-administered propofol for GIE procedures are done.

Nurse-administered propofol

Several studies have documented the safe administration of propofol by nonanesthesiologist personnel. Propofol administration by registered nurses is more cost-effective than administration by anesthesiologists. However, the administration of propofol by a registered nurse supervised only by the endoscopist is controversial because propofol has the potential to produce sudden and severe cardiorespiratory depression. Moreover, the American Society of Anesthesiologists (ASA) guideline on sedation by nonanesthesiologists characterizes propofol as an anesthetic agent that is frequently associated with deep sedation. It does not preclude the administration of propofol by nonanesthesiologists[25]. In contrast, the American Society of Gastrointestinal Endoscopy (ASGE) guideline on deep sedation reaffirms the opinions of the ASA guideline. The ASGE guideline does not recommend the use of propofol for routine GIE procedures[45].

Safety and efficacy of propofol administered by registered nurses has been reported in a case series including 2000 patients undergoing elective esophagogastroduodenoscopy and/or colonoscopy[46]. Five episodes of oxygen desaturation to <85%, four of which required temporary mask ventilation, occurred. Four of these episodes occurred during upper endoscopy. Consequently, administration of propofol by registered nurses is more cost-effective than administration by anesthesiologists. However, More information is needed on how training nurses and endoscopists should proceed to give propofol as well as the optimal level of monitoring to ensure the safety of nurse-administered propofol[47]. Other studies also demonstrated that the risk of colonic perforations during colonoscopy was not found to be significantly higher in patients undergoing nurse-administered propofol compared to patients undergoing conventional sedation, although a tendency may exist[48].

Gastroenterologist-administered propofol

Similar to qualified nurses, the gastroenterologist can administer

propofol effectively. However, the qualified nurses and gastroenterologists must have a thorough knowledge of the pharmacology of the agents used for sedation and the training necessary to recognize and manage oversedation. The importance of preprocedural assessment and preparation as well as appropriate monitoring cannot be overlooked. Many guidelines recommend that gastroenterologist and nurse-administered propofol should be sedated the patients only in mild or moderate (conscious) sedation level. Additionally, the patients must have ASA physical status not more than III. Vargo and colleges completed a randomized, controlled trial of gastroenterologist-administered propofol *vs* meperidine and midazolam for elective ERCP and EUS. Capnography was used to detect apnea or hypercapnia. This study shows that propofol leads to significantly improved recovery of baseline activity and food intake 24 h after the procedure. The authors suggest that propofol would be more cost-effective than meperidine and midazolam for ERCP and EUS procedures[49].

Several procedure-specific risk factors for cardiopulmonary events during propofol-mediated GIE procedures are identified. However, there is no difference in the risk between monitored anesthesia care and gastroenterologist-administered propofol in with ASA class III or greater[50]. The safety of the balanced propofol sedation administered by gastroenterologists during endosonography with fine needle aspiration procedures was demonstrated. No major complications related to sedation were registered during all these procedures[51]. In addition, patients undergoing advanced upper endoscopic procedures and monitoring with graphic assessment of respiratory activity, received a propofol infusion under the control of a qualified gastroenterologist can detect early phases of respiratory depression, resulting in a timely decrease in the propofol infusion without significant hypoxemia, hypercapnia, hypotension, or arrhythmias, and the satisfaction scores are extremely high[52].

FOSPROPOFOL

Fospropofol is a water-soluble prodrug of propofol that currently approved for sedation and analgesia for diagnostic and therapeutic procedures. As a prodrug of propofol, fospropofol's pharmacologic activity results from its breakdown by alkaline phosphatase and release of propofol, which is the active molecule. It exhibits a longer time to peak clinical effect and a more prolonged action compared to propofol[53]. Fospropofol is characterized by a smooth and predictable rise and decline rapidly observed following intravenous administration. Thus patients may exhibit smoother hemodynamic and respiratory depression compared to propofol lipid emulsion bolus. Another advantage over propofol is that it does not cause pain on intravenous injection.

Similar to propofol, fospropofol causes dose dependent hypotension, respiratory depression and apnea[54]. Side effects include perineal paresthesia and itching, respiratory depression, hypoxemia, hypotension, loss of consciousness, and apnea with higher IV boluses. Therefore, current recommendations call for it to be administered only by clinicians trained in general anesthesia, who are skilled in advanced airway management. Fospropofol is currently approved for use in the US for monitored anesthesia care sedation in adults undergoing diagnostic or therapeutic procedures[53]. No studies have been conducted in patients aged <18 years. Phase II and III clinical trial data indicate that fospropofol is effective and generally well tolerated when used for its approved indication.

Clinical uses

Fospropofol has a unique dosing regimen, with a standard dose for adults 18-65 years of age, and a modified dose for patients >65 years of age and for sicker adult patients. The minimum and maximum IV bolus doses are body-weight adjusted to 60 and 90 kg respectively. Available evidence demonstrates the clinical efficacy of fospropofol in sedation of patients undergoing diagnostic or therapeutic GIE procedures[55]. The use of fospropofol is also now being explored in many other perioperative settings. However, fospropofol can take the place of propofol in the intensive care unit and operating room remains to be determined.

Its onset of sedation is approximately 3-8 min and has a duration of 20-30 min. Once fospropofol is converted to propofol, its elimination half-life is the same. Fospropofol also lacks the drug formulations concerns of bacterial growth, need for preservatives, egg product allergies, drug separation, and intense irritation on injection associated with propofol[56]. Incidences of respiratory depression in fospropofol studies have been associated with prior fentanyl administration. Some practitioners administer fospropofol during endoscopy setup, but after monitoring has begun, so that the onset of effect is timed well for procedural start. Under standard dosing regimen, the recommended initial dose of fospropofol is 6.5 mg/kg as an IV bolus injection, followed by the supplemental doses of 1.6 mg/kg and no more frequently than every 4 min as needed to re-establish sufficient sedation depth in adults undergoing diagnostic or therapeutic procedures. Elderly patients and patients with severe systemic diseases should receive the modified dosing regimen, which equates to 75% of the initial and supplemental doses[57].

DEXMEDETOMIDINE

Dexmedetomidine is a specific central α_2 adrenergic agonist that decreases central presynaptic catecholamine release, primarily in the locus coeruleus. Its potency is eight times greater than clonidine. Dexmedetomidine has no effect at the GABA receptor, and unlike other sedatives, it is not associated with significant respiratory depression. Its properties of sedation, anxiolysis and analgesia together with its favorable pharmacokinetics make it a valuable adjunct for procedural and intensive care sedation. It can be used as a total intravenous anesthetic in doses up to 10 mg/kg/h and is approved for use in the USA for sedation in the intensive care unit for up to 24 h. Its properties make it an interesting drug for research, potentially widening its scope of use.

The reason why dexmedetomidine possesses anesthetic/sedative properties is that is a 2-adrenoceptors are present in the brain, involved in antinocceptive, sedative, sympatholytic and hypothermic functions. Like other a 2-adrenoceptor agonists, dexmedetomidine induces a biphasic blood pressure response: high doses cause hypertension via a 2b-receptors on vascular smooth muscle, which precludes rapid intravenous injection. Lower doses cause hypotension and bradycardia by a centrally-mediated reduction in sympathetic activity. This effect is argued to contribute to cardiac protection in the perioperative period. Furthermore, dexmedetomidine does not appear to depress respiration. Intravenous dexmedetomidine may have some analgesic properties, probably with the spinal cord as its main site of analgesic action.

Pharmacologic considerations

Onset of action of dexmedetomidine is about 5-10 min with a dose-dependent duration of 1-2 h. Dexmedetomidine has a distribution half-life of 6 min and terminal half-life of 2 h. The volume of distribution is less than 1 L/kg. It is metabolized through glucuronidation and cytochrome P-450 by the liver. Before administration as either a loading dose or maintenance infusion,

dexmedetomidine must be diluted in 0.9% sodium chloride to achieve a concentration of 4 mcg/mL. For procedural sedation, a loading dose of 1 mcg/kg infused over 10 min is given followed by a maintenance infusion of 0.2-1 mcg/kg/h titrated to the desired effect. This dose should be reduced in elderly patients and patients with hepatic dysfunction.

Cardiorespiratory effects

As dexmedetomidine inhibits norepinephrine release from presynaptic neurons, the most common adverse effects associated with its use for procedural sedation are hypotension and bradycardia. A subset of patients may actually experience transient hypertension due to peripheral vasoconstriction during the loading dose. Rebound hypertension and tachycardia have not been described upon cessation of dexmedetomidine. Patients who are on a continuous infusion of dexmedetomidine for an extended period of time can experience withdrawal symptoms after withdrawal such as nausea/vomiting, agitation, tachycardia and hypertension. This is usually not seen when dexmedetomidine is used for procedural sedation. It causes minimal respiratory depression when used at recommended doses.

Clinical use

Dexmedetomidine is currently approved for use only for less than 24 h. It is also approved for sedation of nonintubated patients before and/or during surgical or other procedures such as interventional radiology procedures and awake fiberoptic intubations. It provides a more wakeful sedation than other sedatives. Patients are more arousable and alert when stimulated. Dexmedetomidine should be avoided in patients whose clinical stability is dependent on high resting sympathetic tone because it decreases central sympathetic outflow. It may also have analgesic effects[58]. However, it does not have amnestic properties so another agent would need to be used in addition to or instead of dexmedetomidine, if this property is desired. The most common adverse effects from its use are nausea, dry mouth, bradycardia and varying effects on blood pressure. Slowing of continuous intravenous infusion may help to prevent or lessen the hypotensive effects[56].

The role of dexmedetomidine for sedation in GIE procedure is not entirely established. The studies about dexmedetomidine suitability for GIE procedure have controversial results. The study of Dere and colleges showed that dexmedetomidine provided more efficient hemodynamic stability, higher Ramsay sedation scale scores, higher satisfaction scores and lower pain scores in colonoscopies[59]. Consequently, sedation with dexmedetomidine is effective and safe for sedation in therapeutic GIE procedure such as endoscopic submucosal dissection[60]. However, some studies were demonstrated that dexmedetomidine alone was not as effective as propofol combined with fentanyl for providing conscious sedation during an ERCP procedure. Furthermore, dexmedetomidine was associated with greater hemodynamic instability and a prolonged recovery[61]. In addition, the study of Jalowiecki and colleges also showed that the use of dexmedetomidine to provide analgesia/sedation for colonoscopy was limited by distressing side effects, pronounced hemodynamic instability, prolonged recovery, and a complicated administration regimen[62]

KETAMINE

Ketamine is a white crystalline solid, which is soluble in water and is stable at room temperature. Termination of the anesthetic action is due to redistribution. The major pathway of hepatic metabolism is norketamine. Norketamine has about 30% of the activity of ketamine. Ketamine is a neuroleptic anesthetic agent that works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors. This results in a dissociative anesthesia characterized by catalepsy in which the eyes remain open with a slow nystagmic gaze, while corneal and light reflexes remain intact. It exists as a racemic compound containing equimolar amounts of the enantiomers. S(+) ketamine has a fourfold greater affinity for NMDA receptors then does R(-) ketamine. In the clinical study, the recovery time is reduced with S(+) ketamine compared with the racemic mixture. S(+) ketamine is more potent and associated with fewer adverse effects than R(-) ketamine. However, the racemic mixture is not available in Thailand[63].

Pharmacologic considerations

Ketamine may be given through intravenous or intramuscular routes. When given intravenous (IV), the onset of action is rapid at 30 sec with a duration of 5-10 min as opposed to an onset of action of 2-4 min and duration of action of 15-60 min for intramuscular (IM) injection. Dosing for IV ketamine includes 1-2 mg/kg bolus, followed by 0.2-0.5 mcg/kg every 10 min until the desired effect. Dosing for IM ketamine includes 4-10 mg/kg bolus followed by 2-4 mg/kg every 15 min for the desired effect. Premedication with low-dose benzodiazepines has been shown to reduce the likelihood of recovery agitation[64].

Ketamine has high lipid solubility and low protein binding, resulting in rapid transfer across the blood-brain barrier. When ketamine undergoes hepatic biotransformation through the cytochrome P-450 system and N-demethylation, an active metabolite, norketamine, is produced. Norketamine exhibits approximately one third the potency of the parent compound. Elimination is primarily by the kidney with an elimination half-life of 2 h.

Cardiorespiratory effects

Ketamine differs from most sedative and analgesic agents as it is known to stimulate the cardiovascular and respiratory systems. This results in a direct increase of cardiac output and systemic arterial pressure, heart rate as well as pulmonary arterial and central venous pressures. All these effects are related to sympathetic stimulation, with increased circulating concentrations of catecholamines. Ketamine has been shown to directly depress myocardial contractility, the negative inotropic effect is masked by induction of the central nervous system. This sympathomimetic effect is expected to increase myocardial oxygen demand. Therefore, it is a valuable induction agent for hypotensive or hypovolemic patients, but these effects make it less desirable in patients with ischemic heart disease or raised pulmonary vascular pressures.

Respiratory depression is minimal and bronchodilatation occurs. These effects are potentially useful in patients with reactive airway disease. Ketamine also maintains the functional residual capacity, decreasing the chance of intraoperative hypoxia. However, ketamine can also stimulate tracheobronchial secretions and excessive salivation. Anticholinergic agents such as atropine may be given to blunt this effect[64]. Pharyngeal reflexes are being preserved, and the upper airway remaining relatively patent with ketamine. However, laryngeal reflexes remain active, the risk of laryngeal spasm, regurgitation and aspiration are still possible. Rapid IV administration of ketamine should be avoided due to the risk of apnea. When given IV, the administration should be over 60 sec.

Clinical use

Ketamine produces analgesia, a dissociative anesthetic state,

and unpleasant postoperative psychomimetic effects including hallucinations and nightmares. At subanesthetic concentrations, ketamine produces good analgesia due to suppression of spinal cord activity via an effect on opioid k-receptors. However, nausea and vomiting are relatively common. Ketamine induces psychomimetic activity and emergence reactions in up to 30% of patients. These adverse reactions may be lessened by preoperative discussion with the patient and some medications. Benzodiazepines are probably the most effective drugs for attenuating psychic reactions.

Ketamine is associated with bronchodilation, cardiorespiratory stability, and preservation of airway reflexes, making it ideal for use in battlefield surgery and in hypovolemic patients. Sympathetic stimulation can be troublesome in patients with ischemic heart disease. It causes an increase in cerebral metabolic rate, blood flow and intracranial pressure. The recent studies have shown a benefit of ketamine in the treatment of status epilepticus. Ketamine is also commonly used for sedation during regional anesthesia, sedation of uncooperative patients, analgesia during burn dressings, and for postoperative pain relief in patients with chronic pain. Despite an extensive list of adverse events and pharmacologic targets, ketamine is safe and effective when used in appropriate populations. Because of its unique profile, it may provide an ideal alternative for patients presenting with hemodynamic instability requiring procedural sedation. Ketamine should be avoided in patients with severe cardiovascular disease, cerebral spinal fluid obstructive states, elevated intraocular pressures, high predisposition to laryngospasm, and history of airway instability.

Ketamine alone or in combination with other sedative agents has been for sedation in adult and pediatric patients. In difficult-to-sedate adult patients, ketamine provided deeper sedation and faster recovery than additional doses of meperidine and diazepam in the patients who were inadequately sedated during advanced GIE procedures such as ERCP and EUS[65]. Moreover, sedation with combination of ketamine, midazolam, pentazocine and propofol resulted in improved patient tolerance compared with propofol alone during ERCP procedure[66]. The combination of ketamine, propofol and low dose remifentanil for ERCP outside the operating room confers clinical advantages because it avoids deep sedation, maintains adequate analgesia with conscious sedation and achieves lower incidence of postprocedural nausea and vomiting with shorter discharge times[67].

KETOFOL

Ketofol is the combination of ketamine and propofol in various concentrations. Ketofol has established itself as a useful combination in procedural sedation around the world. The combination of propofol and ketamine with opposing hemodynamic and respiratory effects, may lead to smaller dosages of each drug, which may lead to less dose related side effects, plus a possible synergistic effect, which makes this combination so interesting. In addition, the combination of these two agents for procedural sedation may preserve sedation efficacy while minimizing their respective adverse effects. This can be partly because most side effects are dose dependant and when used in combination the doses of each should be reduced[68]. The advantage of ketofol producing a more stable hemodynamic and respiratory profile was tested during several studies.

The goal of procedural sedation is to provide an adequate level of sedation while minimizing pain and anxiety, maximizing amnesia, minimizing the potential for adverse drug-related events, controlling behavior, and maintaining a stable cardiovascular and respiratory status. The ideal pharmacologic agent for procedural sedation would accomplish all of these goals, and would have a quick onset and offset, be safe in all age groups, be inexpensive, and be equally efficacious in multiple routes of administration. The incentive to use procedural sedation has the benefit by combining analgesia and sedation. Ketamine is a good alternative agent for general anesthesia and addition to any painful procedure where no sedation is offered.

Ketamine and propofol are physically compatible with no increase in particle content at Y site of injection. Ketofol solutions have been found to be stable up to 3 h when stored at room temperature with exposure to light in 50:50 and 30:70 proportions[69]. Consequently, ketofol has proved to be a safe and effective sedative. Its use provides not only a good position comfort, possible avoidance of opioids and no effect of ketamine on psychomotor recovery, but also a more controlled sedation than when these agents are used in the same doses alone[70]. If ketofol is used alone, it is adequate for minor procedures. The author commonly uses low dose ketamine in combination with low dose midazolam, opioid drug, and/or low dose of propofol[27,71]. The recommended preparation of ketofol for pediatric use is a 50 mg of ketamine and a 90 mg of propofol diluted to 10 mL. This result in a concentration of 5 mg/mL ketamine and 9 mg/mL propofol and, of this solution, 0.005 mg/kg is recommended[72].

The negatives of propofol, which as mentioned, includes a painful infusion, transient cognitive dysfunction, cardiovascular and respiratory depression and the absence of any analgesic effect. This is contrast with ketamine, which as a dissociative sedative, act as local anesthetic as well as systemic analgesic, has amnestic properties that also preserves muscle tone and protects airway reflexes and spontaneous respiration. Ketamine on the down side has side effects which include the emergence phenomena, postoperative dysphoria, vomiting, or laryngospasm, where the antiemetic effect of propofol, and its anxiolytic effect, together with the use of lower dosages, should decrease these side effects, thus theoretically balancing each other out when used together.

GUIDELINES ON GASTROINTESTINAL ENDOSCOPIC SEDATION

American Society of Anesthesiologists systematically developed the practice guidelines for sedation and analgesia by nonanesthesiologists. These guidelines are designed to be applicable to procedures performed in a variety of settings by practitioners who are not specialists in anesthesiology. Individuals responsible for patients receiving sedation should understand pharmacology of the sedative agents that are administered and the role of pharmacologic antagonists for opioids and benzodiazepines. At least one person capable of establishing a patent airway and positive pressure ventilation should be present whenever sedation is administered. In addition, an individual with advanced life support skills be immediately available for moderate sedation and within the procedure room for deep sedation[25].

The Multisociety Sedation Curriculum for Gastrointestinal Endoscopy (MSCGE) provides a framework for developing an individual plan of study and growth that should be tailored to meet the needs of each trainee based on the strengths and special qualities of each training program. It also can serve the practicing gastroenterologist in the updating of both knowledge and skills required for the practice of procedural sedation for GIE procedure. The MSCGE represents a joint collaborative effort among the American Association for the Study of Liver Diseases, the American College of Gastroenterology, the American Gastroenterological Association Institute and the American Society for Gastrointestinal

Endoscopy. In addition, the Society for Gastroenterology Nurses and Associates played a crucial role in the development of the MSCGE[73].

In European countries, sedation management in GIE procedure varies between countries according to the different legal frameworks and healthcare systems. The majority GIE sedation was administered by endoscopists with support from endoscopy nurses. European and national societies have already developed evidence-based and consensus-based guidelines for sedation and monitoring in GIE procedure that give a comprehensive outline of structural requirements, sedative medication, patient monitoring and discharge as well as the role of endoscopy staff[74]. Numerous studies have shown the efficacy and safety of propofol sedation by non-anesthesiologists in GIE procedure. However, this issue remains highly controversial. Three European societies including the European Society of Gastrointestinal Endoscopy (ESGE), the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) and the European Society of Anesthesiology (ESA) have endorsed the guideline of nonanesthesiologist administration of propofol for GIE procedure[75].

SUMMARY

Sedative and analgesic drugs are commonly used in current medical practice including GIE procedure. Their safety profile is dependent on their pharmacokinetic and pharmacodynamic profiles, patient co-morbidity and the experience of the physician using them. However, all sedative and analgesic drugs have potential to cause severe cardiorespiratory depression, and therefore they should be used with standard physiological monitoring. Effective sedation and analgesia during GIE procedure not only provides relief of pain and suffering, but also frequently facilitates the successful and completion of the procedure. Patients should be closely monitored to prevent oversedation and transition to deep sedation. In addition, deep sedation would require an increased level of care. Understanding situations in which patients are at increased risk is essential.

Understanding the metabolism and excretion of these agents is also important. Patients with renal or hepatic disease are at particularly high risk for drug and metabolite accumulation. Careful titration to the desired effect will avoid oversedation. Moreover, allowing time to relapse between repeat doses will allow for the drug to reach peak effects without causing inadvertent adverse effects. Use of opioid and benzodiazepine antagonists should be judicious and reserved for the patients in cardiorespiratory distress. Importantly, appropriate preprocedural evaluation and preparation of patients, monitoring of physiological functions during sedation as well as early detection and therapeutic intervention need to be done. Therefore, the sedative and analgesic drugs used for GIE procedure in this manuscript should be discussed. Most of these drugs are commonly used in recent clinical practice.

Table 1 Sedative, analgesic and antagonist drugs used in the intravenous route in adult patients.

Drugs	Dose	Onset of action
Midazolam	0.015-0.07 mg/kg (1-5 mg)	1-3 min
Propofol	0.25-1 mg/kg Additional dose of 25-75 mcg/kg/min or incremental bolus of 10-20 mg	30-60 sec
Dexmedetomidine	1 mcg/kg and continuous infusion of 0.2-0.7 mcg/kg/h	10-15 min (sedative ffect)
Ketamine	0.2-0.5 mg/kg	1-2 min
Fentanyl	1-2 mcg/kg (max 100-150 mcg)	30-60 sec
Meperidine	0.5-2 mg/kg (max 100 mg)	1-3 min
Remifentanil	0.1-0.3 mcg/kg	30-60 sec
Flumazenil	0.01 mg/kg (up to 1 mg)	1-3 min
Naloxone	1-2 mcg/kg (max 0.1 mg/kg up to 2 mg)	1-3 min

Doses should be titrated starting with the lower recommended dose.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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