

Review paper

Medications Commonly Used for Analgosedation during a Colonoscopy

Jacek Wadelek*

Dartsch Scientific GmbH, Institut für zellbiologische Testsysteme, 49419 Wagenfeld, Germany

Corresponding author: Jacek Wadelek, Anaesthesiology and Intensive Therapy Department, St. Anna Trauma Surgery Hospital, stocer Mazovia Rehabilitation Centre, Warsaw, Poland

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Abstract

Pharmacologically induced sedation and analgesia have become pervasive throughout medical practice to accomplish diagnostic and minor therapeutic procedures effectively and humanely. The aim of sedation and analgesia is to confirm patient well-being and safety and decrease anxiety during colonoscopy. Knowledge of onset time, appropriate dosing frequency, the potential for side effects, and the proper agents to reverse respiratory depression are essential when administering analgesia and sedation for colonoscopy. Controversy still exists as to whether sedation and analgesia are necessary for flexible sigmoidoscopy and colonoscopy. A combination of benzodiazepine and opioid is the most common regimen utilized for colonoscopic sedation. The most commonly used agents include propofol, benzodiazepines, opioids, barbiturates. Propofol, a short-acting anaesthetic agent, has been proposed for use in sedation, with its rapid onset, improved tolerance to the examination, and quicker recovery times. The administration of sedation agents should be titrated to the minimum amount to achieve the desired effect. improved defense against microbial pathogens.

Keywords: analgesics, sedatives, anaesthesia agents, colonoscopy.

Introduction

Practice guidelines for sedation and analgesia vary in different regions of the world [1,2]. The American Society of Anesthesiologists has established such guidelines for use by physicians who are not anesthesiologists. The society considers sedation to be a continuum but does define three different levels [3]. Minimal sedation provides a drug-induced state of anxiolysis during which patients usually respond to verbal commands. Moderate sedation or analgesia, or conscious sedation, is a drug-induced suppression of consciousness during which patients respond purposefully to verbal commands when aroused by the sound of a voice or light tactile stimulation. No interventions are necessary to maintain a patent airway during conscious sedation. Deep sedation or analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after the administration of repeated or painful stimulation. Ventilatory function may be diminished during deep sedation or analgesia. Invasive or painful procedures require deeper level of analgosedation. In deep level of sedation, the patient may be unconscious, unable to cooperate, and have his or her protective reflexes blunted. Deep sedation is usually achieved using intravenous propofol, which has a rapid onset and short duration of action, allowing for reduced recovery time. In Poland, this anaesthetic is also used only by anaesthetists [4-8]. The European guidelines allow for the administration of propofol by

trained nurses or endoscopists who do not complete colonoscopy at the same time [9]. However, this permission only concerns moderate, and not deep sedation. Deep sedation requires specialist equipment and training, and it may be performed only by trained personnel and under appropriate monitoring [10]. The rates of colonoscopies performed by specialised anaesthetic teams increased from 23.9% in 2007 to 53.4% in 2015, respectively, and are still rising [11]. An analysis of anaesthetic-related adverse events registry demonstrated that serious adverse events could occur during deep sedation, even when performed by appropriately trained personnel [12].

Specific agents

The ideal sedative acts predictably and rapidly, inducing a level and duration of sedation appropriate to the procedure being accomplished. An ideal analgesic for colonoscopy will ensure relief of pain to a conscious patient, which will allow for a lively change of patients in endoscopic practice. Such an agent should have a speedy onset and short duration, exhibit analgesic and anxiolytic action, ease of titration to the desired level, quick recovery, and an excellent safety profile with the existence of a specific, rapidly acting antagonist – all this without the need for additional personnel. Drugs used in analgosedation for colonoscopy can be classified into several groups: benzodiazepines,

α 2-agonists, opioids, intravenous anaesthetics and inhaled anaesthetics.

Benzodiazepines

Benzodiazepines are regularly used for intravenous sedation. Benzodiazepines have many pharmacodynamic characteristics that make them ideal medications for conscious sedation including an anxiolytic effect, anterograde amnesia, and sedation. Other class effects include hypnosis, muscle relaxation, and anticonvulsant activity. The commonly used benzodiazepines are midazolam, diazepam, differing in the speed of onset and duration of action. They have a ceiling effect that limits central nervous system depression, but when they are combined with other anaesthetic agents, they can lead to profound respiratory depression. Significant variability in the pharmacokinetics of midazolam and diazepam occur with hepatic disease processes.

Diazepam

Diazepam was the only agent in this group used in the early period of endoscopy, and it is still used for colonoscopy worldwide. Diazepam is insoluble in water, and is commercially available in a solution containing propylene glycol. The diluent, propylene glycol, can result in tissue irritation, pain on injection, and local thrombophlebitis. These problems are not seen with midazolam, which is water-soluble. Recently, diazepam has been made available in a lipid emulsion in an attempt to limit the issues of local tissue irritation and pain on injection. It is used as a single intravenous dose of 5-10 mg [13].

Midazolam

Midazolam is a short-acting benzodiazepine, which is still the most commonly used sedative in colonoscopy. It is 1.5-3.5-times more potent than diazepam. After an IV bolus, the onset of action is in approximately 30 seconds to 60 seconds, the maximum effect is reached in 3 minutes to 5 minutes, and the effect lasts for 20 minutes to 80 minutes. Termination of action is due to redistribution. It is mainly metabolized in the liver. Its duration of action is prolonged in patients with cirrhosis, congestive heart failure, and renal failure. Midazolam administration may sporadically induce paradoxical reactions, such as aggressive behaviour or agitation. It is typically given in a single dose of 30-50 μ g/kg body weight for colonoscopy, followed by intravenous titration to reach the desired level of sedation. Dosage reduction is advised in patients over 60 years of age [14].

Flumazenil

Flumazenil is a specific benzodiazepine antidote that antagonises other benzodiazepine action. It is a competitive inhibitor of GABA. Duration of antagonism is brief and may require repeated doses. It might, however, trigger seizures, acute withdrawal symptoms, nausea, dizziness, agitation, or arrhythmias in addicts. The half-life of flumazenil is 0.7-1.3 hours, and the average duration of antagonist action is 1 hour. Flumazenil lowers the seizure threshold and should be used with extreme caution in settings of benzodiazepine dependence, seizure disorder, cyclic antidepressant overdose, the elevated intracranial pressure in patients, and in patients taking medications known to lower the seizure threshold. Rapid reversal can lead to sympathetic stimu-

lation, and careful titration can allow partial rather than complete reversal.

Dexmedetomidine

Dexmedetomidine is an intravenous agent with sedative, analgesic, anxiolytic, and sympatholytic effects used for procedural sedation in unintubated patients. Dexmedetomidine is an alternative to midazolam for intravenous sedation. It is a highly selective α 2-adrenoceptor agonist with sedative, anxiolytic, and limited analgesic effects. Inhibition of sympathetic outflow from the locus ceruleus in the brainstem results in sedation and anxiolysis. It has a half-life of 2 to 3 hours, and its clearance decreases with hepatic impairment. Dexmedetomidine is the latest drug in this group. The distribution half-life of intravenous dexmedetomidine is about 6 minutes, and the elimination half-life is about 2 hours. Administered as an intravenous bolus of 1 to 3 mg/kg over 10 minutes followed by infusion rates of 1 to 3 mg/kg/h when used as the sole sedative. [15].

Barbiturates

Barbiturates act similar to benzodiazepines, except that they directly act on GABAA receptors and increase the flow of chloride ions into the neuron by prolonging the time the GABAA receptors remain open [16]. Also, barbiturates have a narrower therapeutic index compared with benzodiazepines and are no more effective. Barbiturates produce a dose-dependent progression of sedation, hypnosis, amnesia, and anaesthesia. After IV administration, barbiturates accumulate rapidly in the cerebrospinal fluid and brain tissues leading to their rapid onsets. Duration of action are also short as they rapidly redistribute from vessel-rich groups of tissue to peripheral compartments, such as lipid and muscle [17].

Methohexital

Methohexital is an ultrafast-acting barbiturate. Its pharmacokinetic profile includes an onset of action <45 seconds, duration of 3 to 10 minutes, and shortened elimination. Because of rapid tissue redistribution, the distribution half-life is only 4 minutes with an elimination half-life of 30 minutes to 4 hours (depending on hepatic blood flow and cardiac output). Methohexital is twice as potent as thiopental [17,18]. Methohexital can be used for conscious sedation for short procedures or for induction of anaesthesia to facilitate intubation. An IV dose of 0.75 to 1.5 mg/kg is initially given and can be followed by 0.5 to 0.75 mg/kg every 2 to 3 minutes until desired effect [18].

Thiopental

Thiopental (pentobarbital) is presented as a sodium salt (0.5 g pale yellow powder) to aid dissolution of the drug in 20 ml water (to form a 2.5% solution). The powder also contains 30 mg anhydrous sodium carbonate, and the ampoule is filled with nitrogen (80 kPa; to prevent precipitation of unsolvable free acid by atmospheric carbon dioxide). When prepared, the solution is not stable and should be used within 24-48 hours, but can be kept up to a week in a refrigerator. The solution has a pH of 11-12 (i.e. strongly alkaline and bacteriostatic), and so is incompatible with many drugs, and is also very irritant on arterial injection or extravasation (both can lead to precipitation of non-ionized thio-

pental). Pentobarbital when used in the dose of 1–2 mg/kg, has a rapid onset of action within 3–5 min, with a duration of action between 20 and 40 min.

Etomidate

Etomidate is an imidazole hypnotic agent that has a rapid onset and short duration of action and has fewer hemodynamic and respiratory effects than other sedative-hypnotic agents. Recent studies have reported a high level of efficacy when used for procedural sedation and analgesia, especially for fracture reductions. The dose used varies between 0.1 and 0.3 mg/kg. The lower dose produces a shorter duration of sedation, which is especially useful in some rapidly performed procedures. The commonly reported adverse events with etomidate include myoclonus, vomiting, transient oxygen desaturations, respiratory depression and pain with injection. Transient adrenal suppression has been established for up to 24 h, even with a single dose of etomidate. This effect is caused by a dose-dependent effect via inhibition of the mitochondrial hydroxylase activity in the adrenal glands and does not seem to have much clinical significance with one-time use.

Propofol

Propofol is an intravenous anaesthetic agent of the alkyl phenol group. Because of its insolubility in water, it is commercially available in an egg lecithin emulsion as a 1% (10 mg/mL) solution. Its chemical structure is distinct from that of the barbiturates and other commonly used anaesthetic induction agents. Propofol is an agent with sedative properties with no analgesic component. The gamma-aminobutyric acid accumulation induces sedative effects due to dissociation with its GABA receptor. Propofol has many desirable characteristics for procedural sedation: extremely rapid onset, a substantial potency that reliably produces effective conditions for procedural sedation and analgesia, extremely short recovery (5–15 min), and high satisfaction to patients as a result of its antiemetic and euphoric properties. These properties make propofol a valuable sedative in colonoscopy. The activity of propofol varies depending on the age, body weight, comorbidities and related pharmacotherapy. Even a single dose of propofol can induce deep sedation and short-lasting hypoxic apnoea. Hypotonia may also arise. Propofol is contraindicated in patients with known hypersensitivity to albumins and soy protein [19,20]. Propofol possesses no analgesic properties. Therefore, it should be combined with an opioid when analgesia is required. Other than the passage of time, there is no specific antidote for propofol. Caution is essential during administration to avoid deep anaesthesia. Mostly, a propofol loading dose of 40 mg to 50 mg is given with further smaller boluses (10 mg to 20 mg) to maintain sedation, with a typical total dose between 100 mg and 300 mg. Continuous infusions at 100 mg/h to 200 mg/h have also been used, but most investigators prefer the flexibility of the bolus approach.

Ketamine

Ketamine is a sedative and analgesic agent that is structurally related to phencyclidine. Ketamine is a non-narcotic and non-barbiturate drug. It exists as a racemic compound containing equimolar amounts of S (+) ketamine and R (-) ketamine. The S

(+) ketamine has a fourfold greater affinity for NMDA receptors than R (-) ketamine. A unique feature of ketamine, which makes it particularly attractive for sedation during procedures, is the provision of both amnesia and analgesia. The beneficial properties of ketamine include preservation of cardiovascular function and limited effects on respiratory mechanics. These properties make it an effective agent for the provision of amnesia and analgesia during painful, invasive procedures while allowing the maintenance of spontaneous respiratory function. Notably, there is no correlation between increasing ketamine dosage and respiratory depression. The drug may induce dysphoric reactions (hallucinations, confusion, dreams) upon awakening in about 10–20% of cases. The incidence of these reactions declines after the coadministration of midazolam. As a result of multiple side effects, ketamine is not recommended as a conventional monotherapy in sedation for colonoscopy. Most studies relate to the use of ketamine in combination with midazolam for colonoscopy in children [21,22].

Ketofol

Ketofol is a mixture of ketamine and propofol. There is a synergistic effect between propofol and ketamine, and combination therapy allows the use of lower dose of both drugs, thereby decreasing the likelihood of side effects [23]. If ketofol is used alone, it is adequate for minor procedures. Uses of low dose ketamine in combination with low dose midazolam, opioid drug, and low dose of propofol. This combination technique produces stable hemodynamic effects and can reduce the sedation-related adverse effects [24]. 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.

Opioids

Opioids comprise a mixed group drugs, both natural and synthetic, that bind to opioid receptors to produce their analgesic effects. They include the naturally occurring agents, such as morphine, and the synthetic opioids, fentanyl, alfentanil, sufentanil, and remifentanyl. Opioids produce a dose-related depression of respiratory. The factors that increase the sensitivity to opioids include higher doses, concomitant administration of other central nervous system depressants, anaesthetics, respiratory acidosis, decreased hepatic metabolism, and renal failure.

Pethidine

Pethidine is predominantly an μ -opioid receptor agonist with local anaesthetic properties. For endoscopic procedures, an initial bolus of pethidine (25 mg) is given and is followed by 25 mg every 3 minutes until the desired level of sedation is achieved. It is metabolized by the liver and excreted by the kidney. It has fallen out of favour 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 commencement of action is 1–3 min, peak effect is 5–20 min, and duration of action is about 2–4 hour. Intravenous dose of pethidine in adult patients is 0.5–2 mg/kg with a maximum dose of 100 mg. The major metabolite normeperidine has analgesic ac-

tivity and causes muscle twitching and seizures in patients with renal insufficiency due to accumulation. It is contraindicated in patients who are allergic to pethidine and those who are taking monoamine oxidase inhibitors. The pharmacokinetic profile of the drug makes it unsuited for relatively short-lasting procedures, such as colonoscopy [25].

Nalbuphine

Nalbuphine hydrochloride is a mixed agonist-antagonist opioid with a duration of action of roughly 3–6 hours. Nalbuphine acts as an antagonist at the μ receptor and as an agonist at the κ receptor, resulting in analgesia and sedation with minimal effects in the cardiovascular system [26]. Doses in the range of 0.1–0.2 mg/kg are recommended. The decreased risks of respiratory depression and apnea make nalbuphine suitable for patients with respiratory problems [27].

Fentanyl

Fentanyl is also is predominantly an μ -opioid receptor agonist. It has a fast commencement of action and clearance. It is metabolized by the liver and excreted in the kidneys. Fentanyl and its analogues are potent phenylpiperidine synthetic opioids that exhibit ideal properties of opioids used in intravenous analgesedation. They have a rapid beginning of action with a short half-life, making them ideal agents for use in intravenous analgesedation. Fentanyl, when used in conjunction with benzodiazepines, its effect can be potentiated. A single intravenous dose has rapid onset (30 s) with a peak at 2–3 min and brief clinical duration (20–40 min). Its effects can be reversed with opioid antagonists ie, naloxone. As sedation does not occur at low doses (1–2 μ g/kg) the concurrent administration of a pure sedative—most commonly midazolam—is advisable. Like all opioids, fentanyl can cause respiratory depression. Because of the lack of histamine release with fentanyl, nausea and vomiting are less common than with morphine or pethidine. In colonoscopy, fentanyl is typically combined with a benzodiazepine or propofol. Lazaraki et al. assessed the efficacy and safety of fentanyl alone at a dose < 0.5 μ g/kg in comparison with midazolam at a dose of 2 mg. Fentanyl provided more rapid psychomotor recovery than midazolam. No adverse events were observed in the fentanyl group, whereas a 35% decrease in arterial oxygen saturation was reported in the midazolam group [28,29].

Alfentanil

Alfentanil hydrochloride is an μ -opioid agonist which is ultra-short-acting (5 – 10 minutes). The onset of action is immediate (1 - 2 minutes). Administered at doses of 8 – 40 mcg/kg it is excellent for procedures lasting up to 30 minutes i.e. colonoscopy. The recovery time is comparable to that observed with equipotent fentanyl dosages. Dose dependency allows for accomplishing favourite levels of cooperation and psychomotor activity [30].

Sufentanil

Sufentanil given by intravascular bolus has a rapid onset of action, similar to fentanyl, with rapid redistribution ensuing in relatively short-term duration of action. Elimination half-time is about 3 hours and is linked with clearance (about 13 ml/kg/

minute) which is chiefly dependent on hepatic blood flow. Duration of action is somewhat shorter than for fentanyl although sufentanil is about 5–10 times more potent. Sufentanil is synthetic opioid which has actions and therapeutic effects that are comparable to those of fentanyl. It is more potent than fentanyl and is the most potent opioid in clinical practice, posing a high risk of apnea with bolus administration. Dosing recommendations include bolus dosing of 0.2 to 0.4 μ g/kg or an infusion of 0.2 to 1 μ g/kg/h.

Remifentanil

Remifentanil, an ultra-short-acting opioid, has advantages over other opioids, because of its rapid onset and offset times, making it appropriate for control of pain during colonoscopy, as an opioid remifentanil provides both analgesia and sedation [31]. Non-specific plasma esterases metabolise the drug. Remifentanil is recommended in clinical situations requiring predictable termination of drug effect, due to its rapid elimination lasting 8–10 minutes. A study showed that low-dose remifentanil (0.05 μ g/kg/min) continuous intravenous infusion combined with an intravenous bolus injection of 2 mg midazolam can provide adequate analgesedation and amnesia, as well as reduced colonoscopy-related discomfort compared to intravenous propofol infusion [32]. Caution should be exercised when opiates are combined with other sedatives as the risk of respiratory depression is substantial.

Naloxone

Reversal drugs should not be routinely administered, but should be held in reserve for oversedation or respiratory depression that is more than transient and when the patient does not respond to verbal or tactile stimulation. Resedation after discharge can be avoided by continuing to monitor patients until the effects of the procedural sedation and analgesia drugs. As a pure antagonist of opioid receptors, naloxone reverses the effects of opioids and therefore obliterating reactions such as respiratory depression, miosis, hypotension and sedation. 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. The onset of action is noted 0.5–2 minutes next to intravenous administration, and 3 minutes after intramuscular administration. Usually, the initial single IV dose is 10 μ g/kg body weight. Naloxone ought to be readily available when opiates are used.

Inhaled anaesthetics

Inhaled anaesthetics are currently used as single anaesthetic agents to induce and maintain general anaesthesia, as anaesthetic maintenance drugs following intravenous anaesthesia induction for balanced anaesthesia and sedation.

Nitrous oxide

Inhalation sedation and analgesia apparatus that delivers nitrous oxide must have the capacity of carrying 100% and never less than 25% oxygen concentration at a flow rate fitting to the size of the patient. Apparatus that conveys variable ratios of nitrous oxide >50% to oxygen that covers the mouth and nose

must be used in combination with a calibrated and functional oxygen analyser. Nitrous oxide possesses many of the characteristics of an ideal agent for sedation. It has analgesic effects already at concentrations of 20% and sedative effects at a level of 30-80%. It is used as an agent supplementary to other inhaled or intravenous anaesthetics [33,34].

Sevoflurane

Sevoflurane is a relatively new inhaled anaesthetic. It should be administered only by those accomplished in general anaesthesia. Appropriately calibrated evaporators should be used for sevoflurane dosing to ensure precise control of the concentration of the drug administered. The MAC (minimum alveolar concentration) value for sevoflurane decreases with increasing age of the patient and the addition of nitrous oxide. The dose should be attuned individually, depending on the age and the clinical condition of the patient [35].

Desflurane

Inhalation administers desflurane. It should be applied only by those qualified in general anaesthesia, using specially designed evaporators for use with this drug. Desflurane diffuses into the body more quickly than other inhaled anaesthetics, resulting in more rapid induction of anaesthesia. It is also more rapidly washed out of tissues, allowing for fast recovery and greater flexibility in the depth of anaesthesia [36].

Conclusions

Colonoscopy is a widespread ambulatory and hospital procedure performed for screening, diagnostic and therapeutic purposes. Although combination of an opioid and sedative agent increases patient comfort, the synergistic respiratory and circulatory depressant effects of both these agents may induce life-threatening adverse effects. Careful titration to desired effect will avoid oversedation. Allowing time to relapse between repeat doses will allow for the drug to reach peak effects without causing inadvertent adverse effects.

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