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PROSPECTS

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Analgesic and sedative agents used in the intensive care unit: A review

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Abstract

Pain is a common experience for most patients in the intensive care unit (ICU). In the current study, the advantages and disadvantages of analgesic and sedative drugs used in the ICU are reviewed. An ideal sedative and analgesic agent should have features such as rapid onset of action, rapid recovery after discontinuation, predictability, minimal accumulation of the agent and metabolites in the body, and lack of toxicity. None of the sedative and analgesic agents have all of these desired characteristics; nevertheless, clinicians must be familiar with these classes of drugs to optimize pharmacotherapy and ensure as few side-effects as possible for ICU patients.

KEYWORDS

analgesic, critically ill patient, intensive care unit (ICU), sedative

1 | INTRODUCTION

Pain is a common experience for most patients in the intensive care unit (ICU).[1,2] Pain, restlessness, and anxiety are certainly the most common problems experienced by ICU patients. ICU patients often experience hypoxia, metabolic disorders, pain, delusions, and distress after discontinuation of some medications.[3] Failure to diagnose pain, which subsequently leads to restlessness and disturbances in patients, results in a larger dose of sedatives being administered. Therefore, a systematic and thoughtful approach to detecting and controlling pain in ICU patients is highly recommended. This can be challenging, because many clinical parameters, such as changes in vital signs, may be unreliable indicators of pain. Surgical wounds, vascular catheter insertion, mechanical suctioning, and mechanical ventilation are among the most important causes of pain in ICU patients.[4,5]

The most important goal in managing ICU patients is preventing and controlling their pain and discomfort and to provide effective care. Administration of sedative and

analgesic drugs is essential to optimize patients' comfort and reduce pain and stress, especially for patients requiring mechanical ventilation. However, administration of these medications may result in unprecedented consequences, including side effects of the drugs, delay in the recovery from a critical illness, and threatening the life of the patient, for example, as a result of respiratory suppression.[4,6,7]

To manage pain and anxiety in the patient, a continuous sedation method with low doses of opioids is usually used. The use of the continuous sedation method has been shown to increase the need for mechanical ventilation and the patient's stay in the ICU, whereas the discontinuation of daily sedatives has been shown to reduce the need for mechanical ventilation and the duration in the ICU.[8] Therefore, it is recommended that a sedation method should be used at certain intervals instead of using a deep and continuous sedation method. In addition, recent studies have shown that the use of an "analgosedation" protocol has a better outcome with regard to pain and stress relief than hypnosis-based sedation, and it also reduces the dose of the hypnotic agents that are utilized.[9,10] These studies show that a wide range of sedative agents and methods are used in the ICU, which are sometimes prescribed irrespective of the patient's needs, type of illness, or without an assessment of the patient's pain index. Naturally, this causes a wide range of undesirable side effects. In this review, we discuss the advantages and disadvantages of analgesic (Table 1) and sedative (Table 2) drugs used in the ICU.

2 | ANALGESIA

Opiates are the most widely used drugs for alleviating pain in the ICU.[4,11] They are also used in patients requiring mechanical ventilation due to the fact that opiates suppress the respiratory system and exhibit sedative properties and, therefore, assist the ventilated patient in tolerating the presence of polymeric-based tubes in the airway. In this review, we consider only opiates, since steroidal and nonsteroidal anti-inflammatory agents are not as potent as opiates for this purpose.

3 | OPIATES

Opiates act by stimulation of the μ-, ƙ-, and δ-opioid receptors, which have widespread presence within the central nervous system (CNS) and throughout peripheral tissues.[12] Muscarinic receptors, as the primary source of opiate function, are subdivided into the μ_1 and μ_2-subreceptors. Opiates lead to inhibition of nerve pain by stimulating the μ_1-subreceptors, thus, causing a change in the sensation to pain and the response to pain.

Opiates are classified into 3 categories based on their chemical structure: (a) morphine-like agents (morphine and hydromorphone), (b) meperidine-like agents (meperidine, fentanyl, and remifentanil), and (c) diphenylheptanes (methadone). This review will discuss some of the side effects of opiates, such as hypotension, respiratory suppression, and hypomotility of the stomach and ileus.

4 | MORPHINE

Morphine is one of the oldest opiate agents currently used, and its discovery dates back to 200 years ago. The dose required for morphine to produce analgesic effects depends on the patient's tolerance, metabolism, and ability to excrete the parent compound and its 2 primary metabolites. This agent is the most hydrophilic drug in the group of opiates. Therefore, the onset of morphine administered intravenously (IV) is approximately 5-10 minutes, and the elimination half-life is around 4 hours. It is eliminated via hepatic metabolism, and its metabolites are morphine-3-glucuronide (80%) and morphine-6-glucuronide (20%). The former metabolite does not possess analgesic or toxic properties, while the 6-glucuronidated metabolite is a potent analgesic agent that is 20 to 40 times more potent than morphine.[13,14] The metabolites are excreted through the kidney; therefore, morphine should be used with caution in patients with renal impairment. With patients that have a compromised kidney function, it is suggested that fentanyl be used instead.[15]

In a blinded study, 40 patient in the ICU were randomized to remifentanil or morphine.[16] The results of this study showed that the morphine group had less time in the "optimal sedation" range and, to achieve proper sedation, repeated IV infusion of the morphine was required in these patients. In general, these patients had a longer ICU stay, as well as the time spent intubated and on mechanical ventilation when compared with patients that received remifentanil. The side effects reported with the use of morphine included dysrhythmia (5%), hypotension (5%), and nausea (15%).

Another similar study[9] reported that the use of morphine in ICU patients is likely to increase the duration of mechanical ventilation and prolong weaning time from the ventilator. The side effects reported were similar to those mentioned above: hypotension (5%) and bradycardia (5%).

Impairment of gastrointestinal function caused by the use of opiates remains a serious problem for ICU patients. Many studies have been conducted to reduce this side-effect without losing the analgesic effects of morphine, which includes the use of methylnaltrexone and alumopan.[17,18]

TABLE 1 Pharmacology of analgesics agents

Drug	Mechanism of action	Time to onset (min)	Half-life (h)	Primary metabolic pathway	Presence of active metabolites	Accumulation	Adverse effects
Morphine	μ-Receptor agonist Weak δ-, κ-receptor agonist	5-10	3-4	Glucuronidation	Yes	Decreased metabolism in hepatic failure; active metabolite accumulation in renal failure	Hypotension, constipation
Fentanyl	μ-Receptor agonist	<1	2-4	N-dealkylation CYP3A4/5 substrate	Yes	Decreased metabolism in hepatic failure	Hypotension, constipation, accumulation with hepatic impairment
Meperidine	Weak μ-, κ-receptor agonist	5	3-4	N-demethylation and hydroxylation CYP3A4/2B6 substrate	Yes	Decreased metabolism in hepatic failure; active metabolite accumulation in renal failure	Hypotension, constipation, accumulation with hepatic impairment Seizures, delirium, tremor
Methadone	μ-Receptor agonist Weak NMDA receptor antagonist	Oral: 30 IV: 10–20	9-59	N-demethylation CYP3A4/5, 2D6, 2B6, 1A2 substrate	No	Decreased metabolism in hepatic failure	Constipation, QTc prolongation
Hydromorphone	μ-Receptor agonist	5-10	2-3	Glucuronidation	No	Decreased metabolism in hepatic failure	Hypotension, constipation

5 | FENTANYL AND REMIFENTANIL

Fentanyl and sufentanil are both lipophilic analgesics and, thus, have a rapid onset of action. However, attempts to increase their solubility may potentially increase the extent of distribution and increase the risk of prolonged recovery following long-term administration of these agents. In contrast, remifentanil (a derivative of fentanyl) has a slower onset of action than fentanyl. Remifentanil is metabolized by unspecific esterases, whereas other opiates are hepatically biotransformed and renally excreted. The half-life of remifentanil after IV administration is about 2-3 minutes, while the half-life for fentanyl is reported to be 2-3 hours.

Fentanyl is an analgesic agent that is about 50 to 100 times more potent than morphine. It has a rapid onset of action and is administered by 2 slow IV injections (every 2-4 hours) and continuous infusion.[19] It is also feasible to use fentanyl transdermally in patients who have limited IV access. In 1 study, which evaluated the effects of fentanyl in preterm infants,[20] fentanyl, administered as a single dose, reduced pain in newborns and also decreased changes in the heart rate. The level of growth hormone was also increased following fentanyl administration. However, the use of fentanyl in neonates requires mechanical ventilation for up to 24 hours.[21] Another study suggested that fentanyl has analgesic effects similar to morphine, though the side effects of this agent are fewer than those of morphine.[22]

Comparison of remifentanil with other opioid analgesics and sedatives indicate many advantages of this drug. Muellejans et al[23] compared the efficacy and safety of fentanyl and remifentanil in ICU patients. They concluded that both of these drugs had a good sedative effect, and patients experienced a rapid recovery. Moreover, there appeared to be no significant difference in terms of efficacy and side effects between the 2 drugs. In contrast, the mean time of mechanical ventilation and intubation with remifentanil was noticeably lower than patients administered morphine.[16] Also, in a comparison between remifentanil and midazolam (a short-acting benzodiazepine) in patients requiring long-term mechanical ventilation (up to 10 days), remifentanil significantly reduced the duration of mechanical ventilation (by more than 2 days).[24]

Remifentanil has been shown to have only minor side effects in ICU patients with renal insufficiency and, therefore, it can be concluded that it can be used for sedation and analgesic properties in ICU patients even in cases of organ failure.[25,26]

Following long-term use of fentanyl, side effects such as decreased heart rate, decreased blood pressure, respiratory suppression, digestive disorders, and tolerance

TABLE 2 Pharmacology of selected sedatives

Drug	Mechanism of action	Time to onset (min)	Half-life (h)	Primary metabolic pathway	Presence of active metabolites	Accumulation	Adverse effects	Other effects
Lorazepam	GABAa/BZ receptor agonist	5-20	10-20	Glucuronidation	No	Decreased metabolism in hepatic failure; increased elimination half-life and duration of effect in renal failure; clearance decreases with age	Respiratory depression, hypotension, propylene glycol toxicity, strong correlation with ICU delirium	Hypnotic, anxiolytic, amnestic, anticonvulsant
Midazolam	GABAa/BZ receptor agonist	2-5	3-12	Hydroxylation (CYP3A4/5 substrate)	Yes	Decreased metabolism in hepatic failure; accumulation in renal failure and with prolonged use; clearance decreases with age	Respiratory depression, hypotension, strong correlation with ICU delirium	Hypnotic, anxiolytic, amnestic, anticonvulsant
Propofol	GABAa receptor agonist	1-2	1.5-12.4	Hydroxylation and glucuronidation (CYP2B6 substrate)	No	Increased accumulation with prolonged use	Respiratory depression, hypotension, hypertriglyceridemia, acute pancreatitis, soy and egg allergic reaction	Hypnotic, anxiolytic, amnestic, antiemetic, anticonvulsant
Dexmedetomidine	A2 agonist	15	2	Glucuronidation	No	Decreased metabolism in hepatic failure	Hypotension, bradycardia	Analgesic/opioid sparing, sympatholytic

to the analgesic effects of narcotic drugs are likely to occur.[4,27] The use of opiates by continuous infusion, especially in patients with renal failure who are administered fentanyl or morphine, may be associated with deep sedation. In a study on the effects of remifentanil in patients with brain damage, remifentanil was shown to reduce both blood pressure (14%) and heart rate (6%).[9]

Despite the effects of unspecific esterases as the primary mechanism by which remifentanil is metabolized, it has been reported that the clearance of this agent in patients with renal insufficiency continued to decrease (ie, the half-life of elimination continued to increase) with long-term administration when compared with a group of control patients receiving remifentanil with normal renal function.[28]

Remifentanil acid is one of the fentanyl's metabolites, which undergoes renal excretion and appears to accumulate in patients with renal failure, especially in patients treated with remifentanil for more than 72 hours.[26]

However, due to the fact that this metabolite has very weak opioid activity compared with the parent molecule (remifentanil), the accumulation of this metabolite in the body does not pose a threat of significant side effects[25] and, thus far, no significant side effects have been reported.

6 | MEPERIDINE

Meperidine is more lipophilic than morphine. Thus, meperidine has a faster onset of action than morphine (3-5 minutes). In addition, meperidine has a shorter duration of action than morphine due to its redistribution in various tissues (1-4 hours). Meperidine is metabolized by the liver and is subsequently excreted by the kidneys. Normeperidine, as the main metabolite of meperidine, is a potent CNS stimulant and contributes to seizures, especially in patients with renal failure.[29,30]

The use of meperidine in the ICU patient in not recommended due to its low analgesic potency relative to other opiates, its adverse effects, and especially in view of its CNS-stimulating effects that may induce seizures, delirium, and tremors.[4,31]

7 | METHADONE

Methadone is a synthetic drug with a very long duration of action that can be used to treat chronic pain. Methadone is recommended when the patient is resistant to other opiate drugs. It can also facilitate the "downward-titration" of other opiates in ICU patients to achieve an overall reduction in the amount of opiates being administered to the patient.[32,33] It is typically prescribed for oral administration. Following oral administration, the onset of action of methadone is 30 minutes, with a maximum effect being attained in about 2.5 hours.[34] The mean half-life of elimination is approximately 22 hours but can range from 15 hours to as long as 60 hours, although the duration of its analgesic effect is typically from 4 to 8 hours. The wide variability in its rate of metabolism (range of 4-190 hours) is due primarily to the genetic variability in patients with regard to cytochrome P450 isoenzymes, most notably, variations in the activity of CYP3A4, CYP2B6, and CYP2D6.

Methadone can be used in the treatment of neuropathic lesions, as well as in cases of opiate drug resistance, due to its antagonistic effects on N-methyl-D-aspartate receptors. In these cases, the dose of methadone administered should be lower than the usual dose and should be used as a single dose. Administration of methadone can lead to prolonged QTc (Q-T interval corrected); therefore, when using this drug, it is necessary to monitor the patient frequently for any changes in heart rhythm. When the QTc exceeds 500 milliseconds, the patient's life may be at risk due to the increased chance of developing torsades de pointes.[15,35,36] Like other narcotics, long-term use of methadone may also reduce gastrointestinal motility and induce various digestive disorders. If these symptoms appear, the use of methyl naltrexone can help to reduce these undesirable effects of methadone on the digestive tract.[17]

8 | HYDROMORPHONE

Hydromorphone is an opiate that is classified as a pseudomorphine type drug and has sedative-analgesic effects on the CNS. This drug is another muscarinic receptor agonist, which is used to manage the pain experienced by ICU patients. The bioavailability of this drug is 24% after oral administration, so it is typically administered IV either in a continuous fashion (infusion) or as intermittent bolus injections. The onset of action is about 5-15 minutes, and its half-life is 2-3 hours. Similar to morphine, this agent is metabolized by the glucuronidation pathway in the liver, but unlike morphine, the metabolites of hydromorphone are inactive in terms of analgesic activity but might cause neurotoxicity.[37]

Using hydromorphone at too high a dose can cause acute hydromorphone poisoning, severe hypotension, severe CNS and respiratory depression, and death. Thus, hydromorphone should be used with extreme caution when other CNS suppressive agents are being used concomitantly. In case of acute poisoning, naloxone can be used as an antagonist to reverse the effects of this high-potency sedative-analgesic.[38,39]

Hydromorphone has been referred to as the analgesic drug of choice in patients after renal transplantation owing to its pharmacokinetic advantages over morphine. Hydromorphone has a rapid distribution to the brain tissue, and this characteristic reduces the formation of glucuronide metabolites that need renal excretion; hence it is preferred in patients with renal transplant or impaired renal function.[40] With respect to hepatic dysfunction, it has been shown that the oral bioavailability can be increased by 4 folds in patients with moderate hepatic impairment, yet the half-life of drug was not found to be altered.[41] The pharmacokinetic properties of hydromorphone in patients with severe liver disease need to be studied.

In summary, hydromorphone is one of the best narcotic analgesic agents for controlling the pain experienced by ICU patients due to its short duration of action, high potency, lack of active metabolites, and hemodynamic stability.

9 | SAFETY OF OPIOIDS

Typically, ICU patients experience side effects from the use of opiates.[42,43] Opiates can cause respiratory suppression in a dose-dependent manner, which is very dangerous for patients who have not undergone intubation. These agents also cause nausea and vomiting due to stimulation of the chemoreceptor trigger zone, although this is less common in ICU patients. Using fentanyl at high doses leads to muscle rigidity in some patients. In patients who are hemodynamically unstable, have lowered blood volume, or have increased sympathetic nerve tone, the use of opiates can lead to reduced blood pressure. Due to its effect on the release of histamine, administration of morphine results in greater hypotension, bronchospasm, pruritus, urticaria, and flushing. If patients have a suspected allergy to morphine, fentanyl can be used instead.

Methadone may cause deep sedation in cases where the dose is not reduced after the first 5 days, or when methadone is administrated concomitantly with CYP3A4 and CYP2D6 inhibitors. Opiates may also cause agitation, euphoria, anxiety, hallucinations, sleep disturbances, and delirium in ICU patients.[44] Among the opiates, methadone has the least number of deliriogenic effects on patients due to its antagonistic activity of N-methyl-D-aspartate receptors.[45,46]

Gastrointestinal disorders, such as ileal and gastric retention, are other side effects of opiates experienced by ICU patients.[11] To prevent these complications, laxatives are commonplace, and, in cases where the patient does not respond to these agents, opioid antagonists such as methylnaltrexone can be used.[47] Another complication of opiates is urinary retention, but this problem is rarely seen in ICU patients, given the widespread use of urinary catheters.

10 | SEDATION

Sedation is a technique that produce CNS depression by using sedative agents and allows patient care and treatment without physical, physiological, and psychological stress.[48] This medical protocol not only allows tight control of the physiological parameters of the patient, especially in patients with head injury, but also facilitates mechanical ventilation and reduces pain and anxiety in the patient. Drugs used for sedation in patients are divided into 2 groups: sedatives and analgesics. The former produces CNS depression by stimulating gamma-aminobutyric acid (GABA) receptors, and the latter reduces pain.[49] The following is a summary of the sedative drugs used in ICU patients.

11 | BENZODIAZEPINES

Benzodiazepines are sedative agents without analgesic effects that are used in ICU patients due to their sedative, anxiolytic, and hypnotic effects. These effects depend on the degree to which benzodiazepines bind to GABA receptors, with 20% binding associated with anxiolysis, 30% to 50% binding associated with sedation, and 60% binding producing hypnosis.[51]

These medications also cause anterograde amnesia.[52] Benzodiazepines can suppress the respiratory system, in particular, when used in combination with narcotic analgesics. Midazolam and lorazepam are 2 important benzodiazepines, which are commonly used for sedation in ICU patients.[53]

Midazolam is a benzodiazepine agent with a rapid onset of action (0.5-5 minutes) and a short duration of action (2 hours) following a single dose. This agent undergoes extensive oxidation in the liver via the CYP450 monooxygenase enzyme system.[50]

The primary metabolite of midazolam (1-hydroxymethyl midazolam glucuronide) elicits CNS depressant effects and may accumulate in ICU patients, especially in patients with renal failure. In a series of patients who required prolonged sedation (>36 hours), the plasma level of 1-hydroxymethyl midazolam glucuronide was still significantly elevated for 67 hours after discontinuation of midazolam.[54]

Prolonged sedation effects have been reported with midazolam in obese patients or those patients who have reduced serum albumin levels.[50] The rate of metabolism of midazolam decreases when it is coadministered with

agents such as erythromycin, itraconazole, and diltiazem, which affect the metabolism of midazolam by inhibiting key isoenzymes (CYP enzymes) responsible for the oxidation of midazolam. Also, liver dysfunction may interfere with the metabolism of midazolam and result in the accumulation of its metabolites.

Lorazepam is another type of benzodiazepine agent that has a rapid onset of action (15-30 minutes) and a longer effect (6-10 hours) than midazolam after a single IV dose. Lorazepam is metabolized in the liver by glucuronidation and, ultimately, the metabolites are excreted by the kidneys.[55]

Midazolam has a faster onset of action than lorazepam due to its much greater lipophilicity. Also, when these agents are used for a prolonged time period, the side effects of long-term sedation with midazolam are significantly greater than with lorazepam, especially in obese patients due to partitioning (distribution) of the very-lipophilic midazolam into the adipose tissue.[56,57] Accordingly, the Society of Critical Care Medicine (SCCM) recommended in 2002 that midazolam should only be used for short-term sedation (less than 48 hours) and that lorazepam was more appropriate for long-term sedation in ICU patients.[4] However, recent studies comparing these 2 benzodiazepines (midazolam vs lorazepam) have suggested that there was no difference in the time for the patient to awaken between these 2 medications used for sedation in the ICU.[58,59]

Lorazepam formulations typically contain propylene glycol to facilitate drug solubility. Therefore, when lorazepam formulations containing propylene glycol are used as a continuous infusion for an extended period of time, it is worth noting that several reports have suggested the potential for propylene glycol toxicity, metabolic acidosis, lactic acidosis, acute tubular necrosis, and hyperosmolar states.[11] It has also been reported that lorazepam may cause delirium in ICU patients.[60]

12 | PROPOFOL

Propofol (2,6-diisopropylphenol) is a general anesthetic that has been widely used in the ICU in recent years.[61,62] It exhibits sedative, hypnotic, and amnestic properties in a dose-dependent manner.[63] Propofol acts on the GABA receptor. This agent is extremely lipophilic and easily crosses the blood-brain barrier. Therefore, propofol has a rapid onset of action (1-5 minutes).[64] The onset and offset of the pharmacological action of this agent is relatively short, so its use is recommended in patients who need to awake rapidly from anesthesia.[4]

Propofol clearance mainly occurs through the liver and kidneys. Propofol is extensively metabolized in the renal tissue in the form of glucuronidation. Since the renal and hepatic extraction of propofol is very high, clearance of this drug is mainly dependent on the blood flow but not the metabolizing capacity of these organs. For this reason, moderate impairments to the renal or hepatic function do not affect the pharmacokinetics and total body clearance of propofol.[65]

In elderly patients, the dose of propofol should be reduced due to having a reduced volume for tissue distribution, as well as reduced clearance. Propofol elicits no analgesic effects by itself, and, hence, the dose required for opiates used in patients simultaneously receiving propofol increases in contrast to patients receiving benzodiazepines.[63]

The side effects of propofol include pain at the injection site, hypertriglyceridemia, respiratory depression, hypotension, bradycardia, pancreatitis, acidosis, propofol-related infusion syndrome (PRIS), and neuroexcitatory symptoms.[11]

Hypertriglyceridemia is rarely seen in ICU patients who receive propofol and is more likely to occur during long-term administration of propofol, as well as when a patient is simultaneously being administered lipids (especially triglycerides) for caloric nourishment.[66] This agent, like other lipid-based agents, may have immunosuppressant effects.[67]

Another complication of propofol, PRIS, was first described in 1992 in 5 pediatric patients being treated in the ICU. These pediatric patients showed signs of metabolic acidosis associated with bradyarrhythmia and advanced myocardial failure resulting in death. This occurred following a high dose of propofol (>83 mcg/kg/min for more than 48 hours).[68] Since then, 38 other reports of PRIS have been presented with a mortality rate greater than 80%. Clinical symptoms that have been reported for PRIS include rhabdomyolysis, acute renal failure, myocardial failure, bradyarrhythmia, metabolic acidosis, cardiac arrest, dyslipidemias, and hypotension.[69] The risk of PRIS increases significantly in some clinical situations, such as receiving high doses of propofol (over 83 mcg/kg/min), prolonged use of propofol (up to 48 hours), an age greater than 18 years, and concomitant use of catecholamine vasopressors and glucocorticoids.[69-71]

13 | DEXMEDETOMIDINE

Dexmedetomidine is a selective alpha-2 agonist that is used for short-term sedation (less than 24 hours) in ICU patients. Induction of alpha-2 adrenergic receptors, which are adrenergic G-protein coupled receptors, by dexmedetomidine reduces brain noradrenergic neuronal activity and norepinephrine release, which leads to

enhanced activity of GABA. The use of this agent has been suggested for antianxiety, sedation, and analgesic effects without inducing respiratory suppression even when used with opioid drugs in the ICU.[57] Dexmedetomidine is metabolized in the liver, and its metabolites are excreted through the kidneys. Cardiovascular side effects of this drug compound include hypertension and bradycardia when administered as a bolus IV injection, although hypotension has been associated with continuous infusion of dexmedetomidine.[72]

As mentioned above, dexmedetomidine is commonly used for short-term sedation (less than 24 hours), but it has been reported that it can be used for sedation properties for up to 120 hours.[73] In fact, the risk of coma and delirium in patients receiving dexmedetomidine was much lower than in patients receiving lorazepam.[53] However, further studies are needed to clarify its efficacy with regard to long-term sedation.

14 | VOLATILE SEDATION

Volatile anesthetic agents such as isoflurane are used in patients requiring mechanical ventilation. Isoflurane has better and more predictable sedative properties and a rapid awakening time when compared to other sedative agents, such as midazolam and propofol.[74,75]

Initially, volatile anesthetic agents were not recommended for sedation in ICU patients due to the difficulty associated with their delivery, but with continued advancements in technology, in particular, the introduction of the AnaConDa® filter (Hudson RCI, Upplands Väsby, Sweden), their use has been reconsidered for ICU patients.[76] It has been reported that the use of isoflurane administered by this device is a safe and effective procedure for sedation in ICU patients, with awaking times less than 25 minutes compared with midazolam (57-837 minutes).[77]

Although the use of volatile anesthetic agents is currently not allowed in most countries for the sedation of ICU patients, it may be that additional clinical studies will ultimately demonstrate clinical outcomes that are as equally efficacious as IV-administered sedatives.

15 | CONCLUSION

No one should have to endure an overwhelming degree of pain and both physiological suffering and psychological distress when they are a patient in an ICU, since the medical community has analgesics and sedatives to assist with the pain and discomfort of being critically ill. This is not to imply that no degree of pain and suffering might still be experienced by an ICU patient; rather, it is to be interpreted as that a significant reduction in the degree to which the ICU patient experiences pain and suffering can be made. To this end, an ideal sedative and analgesic agent should have features such as a rapid onset of action, rapid recovery after discontinuation, predictability, minimal accumulation of the agent and its metabolites in the body, and lack of toxicity.[78] This review has discussed the advantages and disadvantages of a number of medications currently used in ICU patients to treat pain and provide sedation, but clearly, none of the agents discussed in this review provide every desired feature or property of an ideal analgesic and/or sedative. Nevertheless, depending on the intensity of the physical symptoms associated with the patient's disease or condition, clinicians can, and should, prescribe the best medicines with the least number of side effects to lessen or ease the suffering of their patients in the ICU.

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CONFLICTS OF INTEREST

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