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Postoperative Analgesia and Sedation in the Adult Intensive Care Unit

A Guide to Drug Selection

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Abstract

An essential goal of all critical care physicians should be to maintain an optimal level of pain control and sedation for their patients. This has become increasingly important because of evidence showing that the combined use of sedatives and analgesics may ameliorate the detrimental stress response in critically ill patients. Unfortunately, both pain and anxiety are subjective and difficult to measure, thereby limiting our ability to analyse these states and making management more challenging.

Although there is still a lack of high quality, randomised, prospective, controlled trials comparing agents, monitoring techniques and scoring scales, several societies have come together to publish some clinical practice guidelines for sedation and analgesia. Recommended opioids are fentanyl or hydromorphone for short-term use, and morphine or hydromorphone for longer-term therapy.

Midazolam or diazepam are recommended for sedation of the acutely agitated patient, while lorazepam is recommended for longer infusions. Propofol is preferred when rapid awakening is desired.

The challenge for critical care physicians is to use these medications to provide comfort and safety without increasing morbidity or mortality. Most studies support the use of protocols in order to help achieve these goals. The bottom line is that most protocols end up stressing some common issues. These include daily cessation of drugs to evaluate the patient and frequent reassessment of the level of sedation required by each specific patient.

Much is still unknown about the long-term effects of sedative and analgesic drugs used as infusions that may last from days to weeks to months. Hopefully, as more studies are performed, we will have more defined clinical end-points, newer drugs with rapid onset and offset and no active metabolites, and decreased morbidity and mortality for our patients.

As intensive care therapies have evolved, a greater understanding of the importance of properly treating pain and anxiety has developed. Failure to achieve these endpoints may have deleterious effects. Fortunately, as a result of the development of better analgesics and sedatives and better methods of drug delivery, significant advances have been made in our ability to address these issues.

Consensus recommendations to guide analgesic and sedative therapy in the intensive care unit (ICU) were published in 1995 and then revised in 2002; however, substantial variability in practice still exists. The reasons for this disparity are multi-fold, but the most important reasons are that: (i) no single depth of sedation or single sedative agent is appropriate for every patient and every situation encountered in the ICU; and (ii) we still lack reliable methods for measuring pain and anxiety.

Theoretically, the choice of the ideal drug should be based on pharmacokinetic and pharmacodynamic properties, cost of therapy (including the drug and the required delivery apparatus) and the cost of treating adverse effects; however, the critically ill often have systemic illnesses, multiple organ failure and haemodynamic instability, which limit drug choices. This article discusses complications from inadequate pain and sedation therapy, the assessment of pain and sedation, pharmacokinetic and pharmacodynamic properties of analgesics and sedatives used in today's critical care practice, and some recent practice guidelines on the use of analgesics and anxiolytics in the ICU.

1. Complications from Pain and Anxiety

Under treated pain results in many physiological responses that are associated with poor outcomes.[1] Stimulation of the autonomic nervous system and release of humoral factors such as catecholamines, cortisol, glucagon, leukotrienes, prostaglandins, vasopressin and β-endorphins following injury, sepsis or surgery are known as the 'stress response'. This activation of the sympathetic nervous system increases heart rate, blood pressure and myocardial oxygen consumption, which can lead to myocardial ischaemia or infarction.[2] The altered hormonal mille can lead to hypercoagulability as a result of increased levels of factor VIII and fibrinogen-platelet activity and inhibition of fibrinolysis.[3] The stress hormones also produce insulin resistance, increased metabolic rate and protein catabolism. Immunosuppression is common because of the reduction in number and function of lymphocytes and granulocytosis.[4] Previously, the stress response was considered a homeostatic mechanism that was beneficial but more recent data have shown that this response may be detrimental in part. Many studies have shown that the adequate treatment of pain can decrease the magnitude of these changes that occur

following surgery and thereby decrease some postoperative complications.[5-8]

The ICU environment can lead to psychological difficulties as well. Memories of vivid nightmares, hallucinations and paranoid delusions were prominent in studies of ICU patients after discharge.[9] Patients who have been ventilated, sedated and paralysed have reported experiencing hallucinations, delusions and altered sense of reality.[10] Although some procedures can be explained to the patient in order to relieve some anxiety, unfortunately not all patients who require procedures during the acute stage of illness are in a state receptive to reasoning. These experiences lead some patients to develop post-traumatic stress syndromes after their stay in the ICU.[11] For these patients, effective therapy for anxiety and pain can reduce some of the emotional adverse experiences and decrease the incidence of postoperative neurosis.[12]

2. Assessment of Pain and Anxiety

Pain and anxiety are subject to interpretation. They are difficult to objectify and monitor from one care provider to another unless a standard is developed for assessing and monitoring these states. This is what makes management of sedation in critically ill patients one of the more challenging areas of ICU care.

For pain, the most widely used scale is the visual analogue scale (VAS), where patients point to a point on a horizontal line that is a representation of the spectrum of pain from 'no pain' to 'the worst pain I've ever had'. The scale is simplistic and has a high degree of reliability and validity,[13] but ignores other dimensions such as the qualitative aspects of pain. Not all critically ill patients can use this scale because of the severity of their illnesses. Sometimes, bedside nurses have to use behavioural signs such as facial expressions, movement or posturing, or physiological signs such as tachycardia, hypertension or tachypnea. Unfortunately, none of these methods are exact. They depend on cultural interpretation of pain, and often the type of illness and use of other drugs can alter the haemodynamic parameters.

Monitoring sedation is also inexact and a true gold standard has not been established. The Glasgow Coma Scale is widely used for the assessment of level of consciousness but validity is established only in patients with neurological deficits. A scale that may be more applicable to the medical-surgical ICU is the 6-point Ramsay Scale.[14] The Ramsay Scale is a numerical scale of motor responsiveness based on increasing depth of sedation (table I). Most comparative studies have used the Ramsay Scale but it also has drawbacks. Because it is based on motor response, the scale has to be modified for patients receiving muscle relaxants, and like the assessment of pain; there is no consensus as to what represents an adequate level of sedation in an individual patient. Other scales include the Sedation-Agitation Scale (SAS) and the Motor Activity Assessment Scale (MAAS), but all have similar drawbacks.

On the horizon, the bispectral index (BIS) of the electroencephalogram is known to provide information about the interaction between cortical and subcortical regions.[15,16] BIS, which is based on a score between 0 and 100, is an index of the level of consciousness.[17] It is more often used in the operating room as an index of the degree of sedation during anaesthesia. Recently, attempts have been made to extend the use of BIS into the ICU, but preliminary reports have been conflicting because of muscle-based electrical activity or metabolic or structural abnormalities of the brain in ICU patients.[18,19] More work is required to validate this technique in ICU patients, but the theoretical benefits of a non-invasive monitor of cerebral function are plausible. However, to date no data have been able to show that BIS monitoring when used to assess depth of sedation significantly alters patient outcomes in the ICU.[20] Because of the lack of evidence, routine use of this device was not recommended by the latest clinical practice guidelines.[21]

3. Analgesics

Pain in the critically ill is best treated with a pure opioid agonist. The commonly available opiates all work at the μ-receptor, so the choice of which agent to use should be based on pharmacokinetic charac-

Table I. Scales used to monitor sedation in patients in the intensive care unit

Score	Response
Ramsay sedation scale	
1	Anxious or restless or both
2	Co-operative, oriented and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus
Motor activity assessment scale	
6	Dangerously agitated and uncooperative. No external stimulus is required to elicit movement, and patient is pulling at tubes or catheters or thrashing from side to side or striking at staff or trying to climb out of bed and does not calm down when asked
5	Agitated. No external stimulus is required to elicit movement and attempting to sit up or moves limbs out of bed and does not consistently follow commands (e.g. will lie down when asked but soon reverts back to attempts to sit up and move limbs out of bed)
4	Restless and co-operative. No external stimulus is required to elicit movement and patient is picking at sheets or tubes or uncovering self and follows commands
3	Calm and co-operative. No external stimulus is required to elicit movement and patient is adjusting sheets or clothes purposefully and follows commands
2	Responsive to touch or name. Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is loudly spoken
1	Responsive only to noxious stimuli. Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus (suctioning or 5 seconds of vigourous orbital, sternal or nail bed pressure)
0	Unresponsive. Does not move with noxious stimulus (suctioning or 5 seconds of vigourous orbital, sternal or nail bed pressure)
Sedation-agitation scale	
7	Dangerous agitation. Pulling at endotracheal tube, thrashing, climbing over bed rails
6	Very agitated. Does not calm, requires restraints, bites endotracheal tube
5	Agitated. Attempts to sit up but calms to verbal instructions
4	Calm and co-operative. Follows commands
3	Sedated. Difficult to arouse, follows simple commands
2	Very sedated. Arouses to stimuli but does not follow commands
1	Unarousable. Minimal or no response to noxious stimuli

teristics. In a recent clinical guideline,[21] the recommended choices have been narrowed to morphine, fentanyl and hydromorphone. Since the use of meperidine (pethidine), nonsteroidal anti-inflammatory drugs and mixed opioid agonist-antagonist agents are discouraged because of potential adverse effects, their use is not discussed here. However, drugs such as methadone, a long acting opioid that can be given parenterally or enterally, and ketamine, a sedative drug with analgesic qualities, are discussed at the end of this section because they do have specific advantages in the ICU patient and can be used for the difficult to sedate patient. Table II lists some of the recommended drugs and their minimal suggested dosages for the treatment of pain.

3.1 Morphine

Recommended as the first-line opioid for use in the ICU, morphine, because of its water-solubility, has a delayed peak effect when compared with the more lipid soluble opioids such as fentanyl (30 minutes vs 4 minutes, respectively). Morphine administration leads to venodilation and decreases heart rate through sympatholysis and direct effects at the sinoatrial (SA) node.[22] The primary adverse effect is its propensity to cause respiratory depression. Other adverse effects include sedation, nausea,

ileus and spasm of the sphincter of Oddi. The primary non-receptor based adverse effect from morphine is histamine release, causing hypotension, tachycardia and possibly bronchospasm in susceptible patients. Morphine has an elimination half-life of 2–4 hours. It does have an active metabolite, morphine-6-glucuronide, which may accumulate and cause excessive sedation in patients with renal failure.[23]

3.2 Fentanyl

Fentanyl is the preferred analgesic agent for critically ill patients with haemodynamic instability or those with a morphine allergy. Fentanyl is a synthetic opioid that is 80–100-fold more potent than morphine. Fentanyl has similar opioid receptor based adverse effects as morphine but it does not release histamine. Fentanyl only causes minor haemodynamic changes and does not affect the inotropic state of the heart. Virtually all haemodynamic variables, including cardiac output and systemic and pulmonary vascular resistance, are unchanged after large doses of fentanyl.[24] Rapid administration of large doses may be associated with bradycardia and chest wall rigidity.

Because fentanyl is lipid-soluble, the duration of action with small doses is short as a result of redistribution from the brain to other tissues. Larger cumulative doses become dependent on elimination as opposed to redistribution. The duration of action lengthens and becomes similar to morphine since the elimination half-lives of the drugs are similar. The pharmacokinetics of fentanyl are not significantly altered in the presence of liver or kidney dysfunction.[25] Fentanyl metabolites may accumulate, but they are largely inactive and nontoxic, and the terminal elimination half-life of fentanyl is based on release from tissue stores rather than hepatic elimination.[26] Only with severe hepatic dysfunction and high-dose fentanyl will altered pharmacokinetics be observed.

3.3 Hydromorphone

Recommended as an acceptable alternative to morphine, hydromorphone is a semi-synthetic opioid that is 5–10-fold more potent than morphine. Time to onset and duration of action are similar to morphine. It has minimal haemodynamic effects and does not result in histamine release. Studies have also shown that pruritus, sedation, and nausea and vomiting may occur less with hydromorphone than morphine,[27] and so it can be a good alternative, especially in patients who are unable to tolerate morphine.

Like morphine, hydromorphone is metabolised by conjugation with glucuronide, but it also undergoes reduction via an NADPH (nicotinamide adenine dinucleotide phosphate) reductase to two active metabolites. The metabolites have greater analgesic activity than the parent compound, but are in such small amounts that they are probably insignificant except in the presence of renal failure or large doses over a prolonged time, where their levels may accumulate to toxic amounts.[28]

3.4 Methadone

Methadone is a synthetic opioid agent with morphine-like properties that can be given enterally and parenterally. It is much longer acting than morphine

Table II. Some of the analgesics recommended for patients in the intensive care unit

Drug	Elimination half-life	Peak effect (IV)	Minimal suggested dosage
Morphine	2–4h	30 min	1–4mg bolus
			1–10 mg/h infusion
Fentanyl	2–5h	4 min	25–100μg bolus
			25–200 μg/h infusion
Hydromorphone	2–4h	20 min	0.2–1mg bolus
			0.2–2 mg/h infusion
Ketamine	2–3h	30–60s	1–2 μg/kg/min infusion

IV = intravenous.

and has a similar receptor-associated adverse effect profile, but it is less sedating. The oral bioavailability is 3-fold greater than the bioavailability of oral morphine.[29] Methadone has had a negative stigma given its association with drug abuse and opioid detoxification, and its long half-life makes titration very difficult in most ICU patients. While methadone is not the drug of choice for an acutely ill patient whose hospital course is rapidly changing, it is a good alternative for the patient who has a long recovery ahead and an anticipated prolonged ventilatory wean. Often once things are stable, transition from fentanyl or morphine infusions to methadone via the feeding tube can help simplify care regimens and decrease dependence on infusions.

Methadone, unlike morphine, lacks active metabolites.[30] It is metabolised in the liver and a small portion of it is eliminated in the kidney. Sixty percent is eliminated by nonrenal routes, so it does not accumulate in patients with renal failure.[29]

3.5 Ketamine

Ketamine, a phencyclidine compound, is an intravenous anaesthetic that has analgesic properties. It works via the N-methyl-D-aspartate receptor as well as the μ-receptor.[31] Traditionally, its primary use in the ICU has been during short procedures with intense pain, such as dressing changes and wound debridement in burn patients. An advantage of ketamine is that it causes minimal respiratory depression.

Ketamine increases blood pressure, heart rate and cardiac output by causing the release of catecholamines.[32] Patients who have been critically ill for a prolonged period may have exhausted their catecholamine stores and may exhibit the myocardial depressant effects of ketamine.[33]

Subhypnotic doses of ketamine administered as infusions have been used for patients who are very difficult to sedate with narcotic and benzodiazepine infusions.[34] These low-dose ketamine infusions (<5 μg/kg/min) do not seem to be associated with the usual adverse effects of ketamine such as hypertension, tachycardia, increased intracranial pressure, excessive secretions, and vivid dreams and hallucinations (termed emergence reactions).[34] Tolerance is known to develop with prolonged use of larger bolus doses, but has not been observed at lower dosages because of limited experience. Because of its potential adverse effects, ketamine is not recommended for routine sedation of the critically ill patient but it can be helpful for more difficult situations. Ketamine also has bronchodilatory effects, which could be beneficial during intubation of asthmatic patients.[35]

Ketamine is metabolised by the hepatic microsomal system to norketamine, which is about 20–30% as active as the parent compound. Pharmacokinetic data are sparse for the patient with liver or renal failure, so no dose adjustment recommendations are available.[36]

4. Sedatives

Anxiety in the critically ill is best treated with a benzodiazepine after adequate treatment of pain and correction of any reversible causes such as hypoxia, metabolic abnormalities, treatable neurological abnormalities, infections, renal or hepatic failure, or nonclinical seizure activity.[37] The commonly available benzodiazepines all work at the GABA receptor, so the choice of agent should be based on pharmacokinetic characteristics. In recent clinical guidelines,[21] the recommended choices have been narrowed to diazepam, lorazepam, midazolam and propofol. Other drugs included in this section are haloperidol, which is useful for delirium, and dexmedetomidine, a new α_2-receptor agonist, which is being used for ICU sedation. Table III lists some of the common drugs and their minimal suggested dosages for the treatment of anxiety.

4.1 Lorazepam

Lorazepam, a benzodiazepine 5–10-fold more potent than diazepam, is the preferred agent for the prolonged treatment of anxiety in the critically ill adult. The effects of this agent are similar to those of diazepam, but unlike diazepam, pain on injection or phlebitis is not expected after lorazepam administration. Lorazepam has lower lipid solubility, which explains its longer time to peak effect.[38] Compared

Table III. Some of the sedatives recommended for patients in the intensive care unit

Drug	Elimination half-life	Peak effect	Minimal suggested dosage
Diazepam	20–40h	3–5 min	5–10mg bolus
			Infusion not recommended
Midazolam	3–5h	2–5 min	1–2mg bolus
			0.5–10 mg/h infusion
Lorazepam	10–20h	2–20 min	1–2mg bolus
			0.5–10 mg/h infusion
Propofol	20–30h	90s	Bolus dose not recommended
			25–100 μg/kg/min infusion
Haloperidol	10–24h	3–20 min	2–10mg bolus
			2–10 mg/h infusion
Dexmedetomidine	2h	1–2 min	Bolus dose not recommended
			0.2–1 μg/kg/h

with midazolam, lorazepam is longer acting, causes less hypotension, mediates equally effective anterograde amnesia, is lower in cost and, with prolonged administration, produces more predictable awakening.[39]

Because lorazepam is diluted in propylene glycol, it may be unstable in solution and can precipitate in intravenous catheters and tubing, necessitating a dedicated infusion line. Propylene glycol toxicity, such as acute tubular necrosis, lactic acidosis and hyperosmolar states, has occurred with large doses of lorazepam or prolonged infusions.[40] It has also been reported after only 3 days of use in a patient with renal failure.[41] Alternatively, lorazepam can be given enterally; however, the large doses of propylene glycol can lead to diarrhoea in some patients.

Lorazepam is glucuronidated in the liver to an inactive metabolite.[42] Because this hepatic system is more resistant to the effects of cirrhosis and hepatic failure than the hepatic microsomal system, lorazepam is often the benzodiazepine of choice for patients with liver disease if a benzodiazepine must be used.[43]

4.2 Midazolam

Midazolam is a short-acting, water–soluble benzodiazepine that is lipophilic at physiological pH and rapidly crosses the blood brain barrier. It has a much shorter duration of action than diazepam as a result of rapid redistribution and it is recommended along with propofol as the two agents which should be used for the short-term (<24 hours) treatment of anxiety in the critically ill adult.[21] Midazolam is 2–3-fold more potent than diazepam. The spectrum of adverse effects includes respiratory depression and hypotension, particularly in the presence of hypovolaemia[44] and in large doses. Prolonged infusions sometimes lead to much longer duration of action especially in the critically ill patient as a result of accumulation of the active metabolite.[45] In some patients, the quick offset may lead to paradoxical agitation.[46]

In patients with impaired hepatic clearance, the elimination half-life of midazolam may be prolonged from 2 hours to 4–12 hours.[47] Midazolam is metabolised to hydroxymidazolam, which has minimal activity[48] and is much shorter acting than the parent compound.[49] With long-term infusions, drug-drug interactions may become important. For instance, erythromycin, propofol and diltiazem all can result in unexpected sedation as a result of inhibition of the cytochrome P450 system and delayed midazolam metabolism.[50,51]

4.3 Diazepam

Diazepam has been used extensively in the critical care setting. With single doses, it can provide rapid onset and offset as a result of its lipid solubility and the effects of redistribution from the central compartment.[52] It causes minimal depression of ventilation or circulation, although some critically

ill patients can be very sensitive to the respiratory depressive and hypotensive effects of diazepam. Long-term diazepam use can lead to prolonged sedation from active metabolites and so, like methadone, it has limitations for ICU sedation. Diazepam is useful in the patient who is facing a prolonged hospital course and a slow wean from mechanical ventilation, but who is otherwise stable from the standpoint of other organ function. It provides a useful transition from benzodiazepine infusions to an oral regimen that can be tapered slowly. Because diazepam is insoluble in water and must be dissolved in organic solvents, pain and phlebitis may occur with intravenous injection.

Diazepam metabolism is dependent on hepatic microsomal enzymes and it is metabolised to two active metabolites, N-desmethyldiazepam and oxazepam. In many patients, including the elderly and those with impaired hepatic or renal function, it may have a markedly prolonged elimination half-life and produce prolonged sedation, therefore, diazepam should be used very carefully in these patient groups.[53]

4.4 Propofol

Propofol is an alkylphenol which is insoluble in aqueous solution and is formulated in a 1% emulsion of soybean oil, glycerol and egg phosphatide. It provides 1.1 kcal/ml from fat and should be counted as a caloric source. A 2% formulation of propofol is currently being evaluated by the US FDA. It has excellent sedative and hypnotic properties, but does not provide analgesia. GABA receptors within the central nervous system appear to be involved but the mechanism of action is not completely known. Rapid and predictable levels of sedation are achieved with infusions and recovery is rapid after discontinuation of the drug.[54] Propofol, along with midazolam, has been recommended as an agent for short-term (<24 hour) sedation in the ICU.[21] Boluses may not be tolerated as well as a maintenance infusion in some patients, especially the critically ill, since propofol may lead to hypotension and myocardial depression.

Because of the lipid formulation, fat overload must be carefully monitored in the critically ill patient.[55] The administration of additional lipids with total parental nutrition should be adjusted for the fat content in the propofol infusion.[56] Patients on long-term infusions should be followed for hypertriglyceridaemia and pancreatitis, which have been reported.[57]

Propofol was modified to include the additive ethylenediaminetetraacetic acid (EDTA) to retard growth of microorganisms. A generic formulation has also become available, which contains a different preservative, sodium metabisulfite, and which has a lower pH. Although there are some subtle differences, the FDA basically considers the two formulations equivalent. Because of the concern for infections, propofol bottles and infusion tubing should be changed every 12 hours, and solutions drawn from the bottle should not be kept for more than 6 hours. Propofol may also cause pain upon injection, and it has been associated with metabolic acidosis, rhabdomyolysis and cardiovascular collapse in several patients.[58,59]

Propofol is metabolised in the liver but, because clearance exceeds hepatic blood flow, an extrahepatic mechanism has been demonstrated as well.[60] Because of the extrahepatic metabolism, propofol is still relatively short acting in patients with liver failure. Renal disease does not appear to alter the kinetics of propofol.[61]

4.5 Haloperidol

Haloperidol, a butyrophenone antipsychotic drug, has been used in the treatment of delirium in the critically ill.[62] The intravenous route is preferred in the ICU patient because of better bioavailability and predictability, but it has not been approved by the US FDA for parenteral use. The dose required to control delirium varies widely between patients. A loading regimen starting with a 2mg dose, followed by repeated doses doubling the previous dose every 15–20 minutes has been described for the acutely agitated patient.[63]

Haloperidol has some significant adverse effects. It reduces the seizure threshold, it may precipitate

extrapyramidal reactions, and it may prolong the QT interval leading to torsades de pointes.[64] Haloperidol should be used with caution in patients at risk for arrhythmias (history of cardiomyopathy or heavy alcohol use) and in patients taking other drugs that may prolong the QT interval such as amiodarone or procainamide. Patients receiving haloperidol should be in a monitored setting and daily electrocardiograms should be obtained to follow changes in the QT interval. Significant QT interval changes have been reported with doses as low as 35mg and as rapidly as within minutes of a 20mg intravenous dose.[64]

4.6 Dexmedetomidine

Dexmedetomidine, an α_2-agonist, is a new class of sedative drug that is being introduced for use in the ICU. It binds α_2-receptors 8-fold more avidly than clonidine and is shorter acting.[65] Beneficial properties include marked sedation with only mild reductions in minute ventilation,[66] reduced haemodynamic response to intubation and extubation, attenuated stress response to surgery and potentiation of analgesics.[67] A prospective, randomised study reported that patients in the ICU who received dexmedetomidine required significantly less additional sedative or analgesic medication than did the control patients.[68] In 1999, dexmedetomidine was approved by the US FDA for short-term (<24 hour) infusion as a sedative agent in critically ill patients. It has not been approved for use in Europe.[69] Patients sedated with dexmedetomidine appear tranquil while being readily arousable and interactive when stimulated.[65]

The adverse effects include hypertension, followed by hypotension and bradycardia from inhibition of sympathetic activity in the central nervous system.[69] Because of this, boluses may not be tolerated as well as maintenance infusions in critically ill patients. Elimination may be prolonged in the presence of hepatic dysfunction, but additional data will be necessary to determine whether this drug can be used in patients with renal or hepatic failure.[69]

Dexmedetomidine needs further studying. For instance, not much information exists in terms of its amnestic qualities or in terms of infusions lasting longer than 24 hours. A small number of patients in the British study reported being excessively aware of the ICU environment despite what was perceived as adequate sedation by the staff.[68] Patients with hypovolaemia, bradycardia or low cardiac output may experience a greater likelihood of adverse effects, so proper patient selection is very important.

5. Global Practices

As shown in sections 3 and 4, a wide variety of pharmacological agents can be used for the treatment of pain and anxiety. Although recommendations have been made for sedation and analgesic regimens in the ICU, practice continues to vary widely between different ICUs. Several studies have attempted to characterise international practices by sending out surveys and questionnaires. In Europe, 63% of participants used midazolam often or always for patients requiring sedation, followed by 35% who used propofol and 9% who used haloperidol often or always for ICU patients.[70] The narcotics were more evenly divided, with one-third using morphine often or always, one-third using fentanyl, and one-quarter using sufentanil. Only 43% of the European ICUs used a sedation scale. When a scale was used, the Ramsay scale was used most frequently at 74% of the time.[70]

In Denmark, midazolam and propofol were used more than diazepam (100, 92 and 24%, respectively).[71] For analgesia, the preferred drugs were morphine (94%), fentanyl (76%) and sufentanil (43%). Only 16% of the ICUs used a sedation scale, but they all used the Ramsay scale if a sedation scale was used.[71]

In England, propofol was slightly more popular than midazolam, while almost no ICUs used lorazepam.[72] After 72 hours of sedation, midazolam infusions became more popular. Analgesic usage included morphine, alfentanil and fentanyl, in that order. A sedation scale was used in 67% of ICUs, but while the Ramsay scale was still the most popular, almost a third of the ICUs used another scoring system.[72]

Overall, although differences do exist between countries, most ICUs around the world are using

Table IV. Clinical practice guidelines for sedation and analgesia from the Society of Critical Care Medicine and American College of Critical Care Medicine[21]

Pain
1. An assessment of pain and the response to therapy should be regularly assessed using an appropriate pain scale
2. Therapeutic plans and goals should be developed for all patients
3. Recommended intravenous opioids are: fentanyl for acute distress, fentanyl or hydromorphone for patients with haemodynamic instability or renal insufficiency, and morphine and hydromorphone for longer term therapy
4. Scheduled doses or continuous infusions are preferred over intermittent boluses
5. NSAIDs and acetaminophen can be useful adjuncts, but beware of renal insufficiency or gastrointestinal bleeding
Sedation
1. Treatment of pain and other reversible causes should be conducted before sedating an agitated patient
2. Like pain control, a treatment plan or goal should be established for each patient, and therapy should be assessed with a validated sedation scale
3. Midazolam or diazepam is useful for the acutely agitated patient
4. Propofol is preferred when rapid awakening is crucial, and triglyceride levels should be monitored after 2 days of continuous infusions
5. Lorazepam is recommended for longer infusions
6. Doses should be tapered daily to assess underlying mental status and sedation protocols can be helpful and beneficial
7. Haloperidol is the preferred agent for the treatment of delirium

similar drugs for pain and sedation. Almost all recognised the importance of adequate analgesia and anxiolysis, and very few used neuromuscular blocking agents unless for specific indications. The use of a sedation score seems to be gaining in popularity but a consensus opinion as to what level of sedation will be the optimal goal is lacking. Further work will be needed to see if the use of these scores can improve ICU morbidity and mortality.

6. Practice Guidelines

The Society of Critical Care Medicine (SCCM) and the American College of Critical Care Medicine (ACCM) conducted a review of the literature and in 1995 published clinical practice guideline for sedation and analgesia for the critically ill patient.[73] These two societies have joined with the American Society of Health-System Pharmacists (ASHP) and they have recently published revised clinical practice guidelines.[21] Table IV is a summary of their recommendations.

7. Sedation Protocols

The challenge for critical care physicians using analgesics and sedatives is to provide patient comfort and safety without increasing morbidity and mortality. Because of the variety in practice styles, pathways to standardise patient care have attracted a lot of attention. From a mechanical ventilation standpoint, weaning protocols have been shown to improve efficiency, reduce resource utilisation, improve patient outcomes, reduce overall ICU expenditures and decrease the frequency of tracheostomies.[74]

For sedation there have been two prospective, randomised, controlled trials examining the effects of sedation protocols in the intubated patient. Brook et. al. randomised 321 medical ICU patients to a nurse-implemented sedation protocol or to standard care.[75] They showed that the protocol group had shorter mechanical ventilation times, length of stay and tracheostomy rates. Kress et. al., also studied medical ICU patients, but their protocol group had their sedation infusions interrupted daily for a 'wake-up test' and the sedation was restarted at half the previous dose.[76] The control group did not have scheduled daily decreases in the infusion rate and care was left to the discretion of the ICU team. They found a statistically significant shorter duration of mechanical ventilation and length of ICU stay in the intervention group.

On the basis, in part, of the above data, recent clinical guidelines recommend that sedation protocols should be instituted and that they include daily

cessation and patient-specific targeted goals of sedation and analgesia administration.[21]

8. Conclusion

There has been increased recognition of the importance of adequate analgesia and anxiolysis for patients in the ICU. Although there are practice differences that still exist, we have made large strides in this area of critical care. Many ICUs are moving toward sedation scales that will help standardise our goals for sedation and many intensivists are now calling for sedation protocols that will help standardise the drugs and dosages that are used. Much is still unknown about the effects of these drugs on the mind after infusions that may last from days to weeks to months. Hopefully, as more studies are performed, we will have more defined clinical end-points, newer drugs with rapid onset and offset and no active metabolites, and improved morbidity and mortality for our patients.

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