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Pain management in the critically ill

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The treatment of pain continues to be a major concern in the critically ill patient. Despite advances in pain management, a greater understanding of the mechanisms of pain and advanced methods of analgesic delivery, the treatment of pain is not always a priority on the intensive care unit. Difficulties with pain assessment, in the critically ill ventilated, sedated patient compound the problems of pain management. Physiological signs are difficult to interpret and psychological factors must be considered.

Introduction

Managing pain in the critically ill patient may present particular challenges for recovery and intensive care nursing and medical staff, as the patient may experience pain from many sources. Not only do these patients experience pain from trauma or surgery, they may also undergo invasive procedures. These procedures vary according to the type of recovery or intensive care unit but may include the insertion of endotracheal tubes, invasive monitoring lines, central venous catheters, chest drains, nephrostomy tubes and dialysis catheters. Procedural pain may also be experienced from regular suctioning via the endotracheal tube, from dressing changes and from turning and moving such as when the patient is washed, repositioned in bed, X-rays are carried out or physiotherapy is performed (Puntillo et al 2001).

Physical pain may not be the only consideration, as psychological factors such as fear, anxiety and sleep disturbance may also contribute to the patient's overall pain experience (Macintyre & Ready 2002). The advantages of good analgesia are particularly important in the recovery room and intensive care patient. The ability to deep breathe and cough with minimal pain and discomfort will enhance respiratory function, facilitate physiotherapy, expedite weaning from mechanical ventilation and encourage earlier mobilisation.

Pain assessment

One of the biggest obstacles to pain management in the recovery room patient or in the intensive care unit is pain assessment (Odhner et al 2003). Assessment may be difficult in the sedated and mechanically ventilated patient when considering that the most reliable indicator of pain intensity is the patient's own verbal report (Kwekkeboom & Herr 2001).

Pain assessment tools such as the verbal or numerical rating scales are of limited use in this patient group and alternative methods of assessing pain may need to be used (Caroll et al 1999, Brown 2008). A method often used in assessing pain in the unconscious, sedated and ventilated patient is observation of physiological and behavioural signs (Gelinas & Johnston 2007). Altered physiological signs may include increased blood pressure, heart rate, respiratory rate and sweating. Altered behavioural signs such as restlessness, groaning and facial grimaces may also be useful indicators of the presence of pain.

If altered physiological and behavioural signs are a result of pain, then monitoring of these signs for improvements following administration of analgesics may give some indication of the success of pain relief. However, it is necessary to consider that the patient's physiological and behavioural signs may be altered by other factors such as their level of sedation or drug administration such as inotropic agents which affect the cardiovascular system including blood pressure, heart rate and the underlying pathology, for example, sepsis, heart failure and underlying multi-organ failure (Payen et al 2001).

Measuring and observing physiological and behavioural signs may be a useful adjunct in assessment of the critically ill patient's pain but these are not altogether reliable in isolation. Indeed it has been suggested that they are the least sensitive indicators of pain (Odhner et al 2003), and therefore should be used in conjunction with other methods of assessing pain. Some patients may be able to give a sign such as squeezing the nurse's hand, blinking once for yes and twice for no, or use of coded finger movements (Pasero & McCaffery 2002). For patients who are unable to do this due to heavy sedation or unconsciousness, it may be necessary to assess the likelihood of the patient being in pain (Brown 2008). For example:

- Does the patient have recent surgical wounds?
- Are there any drains or tubes *in situ*?
- Are there fractured bones or abdominal distension?
- Increased sedation requirements may also indicate inadequate analgesia.

There are two important points that may need to be considered in order to successfully assess and treat the critically ill patient's pain: First, an unconscious patient has lost the ability to communicate their pain, but may continue to experience pain. Secondly, sedating patients does not address pain. While sedation may contribute to relieving some of the anxiety associated with their pain, it should be remembered that sedation is not equivalent to analgesia (Kress et al 2002). It is the responsibility of the recovery room and intensive care staff to

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anticipate painful interventions and procedures such as physiotherapy and administer additional analgesia as appropriate.

Analgesia in the critically ill

Opioids

Opioids remain the mainstay of treatment of acute pain in the critically ill patient. Opioids bind to opioid receptors found in the brain and spinal cord where they exert their effects. The different receptors include mu, delta, kappa and sigma receptors. The side effects of opioids are related to the medicine's affinity for a particular receptor and are usually dose-related. Opioid side effects are listed in Table 1.

Morphine

Morphine is still the 'gold standard' by which all other analgesics are measured. It is a mu receptor antagonist and the least lipid soluble of the opioids. Its main metabolites are produced by conjugation in the liver. Morphine 3-Glucuronide has no analgesic action whereas morphine 6-Glucuronide is a potent analgesic (Macintyre & Ready 2002).

Oxycodone

Oxycodone is an opioid with similar properties to morphine but acts on different opioid receptors. Morphine acts primarily at the mu receptors while oxycodone acts primarily at the kappa receptors (Stannard & Booth 2000). The kappa receptors provide analgesia at the spinal level and may cause sedation and dysphoria, however they produce few unwanted effects and do not contribute to dependence. Oxycodone is licensed for moderate to severe postoperative and malignant pain (British National Formulary 2008) and is available as an intravenous preparation. It has three quarters of the potency of morphine, when administered intravenously and is therefore suitable for use in the intensive care unit (Rang et al 2003).

Fentanyl

Fentanyl is a synthetic opioid, is highly lipid soluble, and has no active metabolites. The lack of metabolites makes fentanyl a popular choice of analgesia for critically ill patients. Fentanyl has a faster onset than morphine but single doses have a shorter duration of action due to rapid tissue uptake. Fentanyl can be used in the intensive care unit to treat severe pain where a short duration of action is advantageous (Rang et al 2003).

It is also useful for patients who will undergo mechanical ventilation for short periods such as postoperative recovery and for patients whose neurological status requires regular assessment.

Diamorphine

Diamorphine is a diacetyl derivative of morphine, and there are no differences between diamorphine and morphine, with respect to analgesia and side effects. The greater lipid solubility of diamorphine enables it to cross the blood-brain barrier more rapidly than morphine and therefore exerts its analgesic effects sooner when administered intravenously. The duration of action is shorter than that of morphine, and may be more likely to cause dependence at high doses over long periods (Rang et al 2003).

Pethidine

Pethidine is a synthetic opioid, chemically related to atropine, and therefore may produce some similar effects such as a dry mouth and tachycardia (Trounce & Gould 2000). It is similar to morphine in its pharmacological effects, although its duration of action is shorter. Pethidine is infrequently used on the intensive care unit due to concerns with its active metabolite norpethidine, which may produce hallucinogenic, and central nervous system effects including twitching, tremors and convulsions (Rang et al 2003). However, pethidine is often used for the management of shivering in postoperative and febrile patients.

Table 1 Effects produced at different opioid receptors

Property	Mu (μ) or MOP1	Kappa (k) or KOP1	Delta (d) or DOP1	Sigma (s)
Analgesia	✔	✔	✔	×
Respiratory depression	✔	✔	✔	✔
Euphoria	✔	×	×	×
Dependence	✔	×	✔	×
Gut Motility	✔	×	×	×
Sedation	×	✔	×	×
Dysphoria	×	×	×	✔
Hallucinations	×	×	×	✔
Delusions	×	×	×	✔

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Remifentanil

Remifentanil is an ultra short-acting opioid, which is independent of hepatic and renal function for its metabolism. It is rapidly metabolised by non-specific tissue and plasma esterases, to the extent that no opioid activity will remain 10 minutes after discontinuation of an infusion, at doses used for sedation in the recovery or intensive care unit. It therefore has ideal properties for combined analgesia and sedation in the intensive care unit. It is a profound respiratory depressant, enabling full mechanical ventilation to be tolerated. It can be used or in conjunction with a hypnotic agent such as propofol or midazolam. It is a potent analgesic, so ensures the patient is pain free, as opposed to over-sedated. It allows rapid arousal and recovery from sedation, facilitating daily sedation holds and rapid neurological assessment (Dahaba et al 2004).

Conversely, if a painful procedure is anticipated such as chest drain insertion or percutaneous tracheostomy, plasma levels can be rapidly increased to provide profound analgesia for the duration of the procedure (Gupta & Ravalia 2000). This analgesic effect can be rapidly titrated against patient response. It has a synergistic effect with propofol or midazolam decreasing the total dose of each individual drug and consequently minimising the side effects of the sedative agents, such as hypotension or myocardial depression. This is a particular advantage in the critically ill, intensive care patient.

Remifentanil can cause bradycardia, chest-wall rigidity, profound respiratory depression and dependence. Prior to discontinuation of remifentanil, alternative analgesia must be established. The nature of this will depend on the individual patient, their reason for intensive care unit admission, underlying pathology and elapsed time since surgery or trauma. Remifentanil is metabolised by plasma esterases. Its main metabolite, remifentanil acid, is excreted via the kidneys, and although excretion rates are reduced in renal failure, remifentanil acid has no mu receptor activity and therefore dosage adjustment is not required in renal failure patients and in patients on haemofiltration or dialysis (Pitsiu et al 2004). Similarly, in severe chronic liver disease the pharmacokinetics of remifentanil are not altered, but liver failure patients may be more sensitive to the respiratory depressant effects of the drug (Dershwitz et al 1997).

Remifentanil has been shown to be advantageous in respiratory weaning of long-term intensive care unit patients compared with conventional sedation regimes using longer acting opioids such as morphine or fentanyl. The remifentanil based sedation regime significantly reduced the duration of mechanical ventilation and significantly reduced the time from the start of the weaning process to extubation by more than one day. There was a trend towards reduced stay in the intensive care unit (Breen et al 2005). Remifentanil has facilitated the use of analgesic-based sedation, relieving discomfort from endotracheal tubes, mechanical ventilation and procedures and lines which are an integral part of intensive care unit care. This has reduced the need for hypnotic agents producing awake, co-operative, but most importantly, pain-free patients on the intensive care unit (Park et al 2007).

Ketamine

Ketamine is an N-Methyl-D aspartate (NMDA) receptor agonist and is mainly used as an agent for induction of anaesthesia. However, it is unique among other induction agents as it also acts as a potent analgesic and produces a state known as 'Dissociative Analgesia' (Trounce & Gould 2000). This state may affect memory and cognitive function where the patient may be unaware of their surroundings, but be free of pain (Rang et al 2003). There is good evidence that as an adjuvant to opioids for the treatment of postoperative pain, intravenous ketamine has opioid sparing effects. Further research has found that for patients in severe pain that is not completely relieved with morphine, the addition of intravenous ketamine provided rapid, effective and prolonged analgesia with no obvious side effects at low doses (ANZCA 2005).

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have three major actions:

- anti-inflammatory
- analgesic
- antipyretic (Rang et al 2003).

Although they may provide potent analgesia and have opioid sparing effects, they may not be suitable for use in the intensive care unit due to their side effect profile. Inhibition of the cyclo-oxygenase enzymes COX 1 and COX 2, causes reduced prostaglandin production (Rang et al 2003). Prostaglandins are involved in protection of the gastric mucosa, the aggregation of platelets and the vascular auto regulatory response of the kidneys (Munden et al 2003). The administration of NSAIDs may contribute to platelet dysfunction, impaired platelet aggregation and bleeding, renal dysfunction, sodium and water retention and gastric ulceration. They are also known to cause bronchospasm and should be avoided in asthmatics (Hiscock 1998).

They therefore have limited application in recovery or intensive care patients with renal dysfunction, cardiac failure coagulation problems and respiratory failure.

Paracetamol

The mode of action of paracetamol is poorly understood, but it demonstrates COX 4 receptor inhibition in the central nervous system, providing analgesia and antipyretic properties (BNF 2008). It has a weak anti-inflammatory action but does not inhibit platelet function, is generally free of gastro-intestinal, renal and respiratory side effects and is suitable for use on the intensive care unit. It should be avoided in severe liver dysfunction, when conjugative metabolism by sulphation or glucuronidation may be impaired. Consequent oxidative

Pain is a subjective experience and therefore individual responses to treatment will vary

metabolism results in the production of the toxic metabolite, N-acetyl-p-benzo-quinone imine (NABQUI), which causes centrilobular necrosis. Intravenous paracetamol, (Perfalgan) can reach maximum plasma concentrations within 15 minutes, (the time it takes to infuse the drug) and has 100% bioavailability in comparison to rectal or oral preparations. It also has the benefit of being suitable for patients who are unable to take medication by oral or rectal routes and has opioid sparing properties.

Local anaesthetics

Local anaesthetics can be used for wound infiltration or for infiltration prior to invasive procedures such as chest drain insertion or central venous catheterisation. Local anaesthetics can be infused via intra-pleural catheters, paravertebral catheters, epidural catheters or continuous wound infiltration using conventional or elastomeric pumps. Staff must be aware of toxicity levels of individual drugs and signs of local anaesthetic toxicity must be promptly acted upon. Assiduous monitoring is particularly important in patients with renal or hepatic impairment. The signs and symptoms of local anaesthetic are described by Cox and Cousins (2008) and suggested management is outlined in a recent guideline (AAGBI 2007).

Routes of administration of analgesia in the critically ill

Whichever route of analgesia administration is used to provide pain relief, it should be individualised according to underlying pathology and patient physiology. Pain is a subjective experience and therefore individual responses to treatment will vary. Managing pain in the critically ill may be best achieved using balanced analgesia, the simultaneous use of analgesics from different pharmacological groups producing a greater degree of analgesia than may be achieved by using the drugs individually. This method is often termed 'multimodal analgesia' and common examples are administering an opioid with paracetamol and a non-steroidal anti-inflammatory drug. Such a combination may also produce an opioid sparing effect and reduce the incidence of opioid side effects.

Intravenous infusion

Intravenous administration of analgesics provides the most reliable and rapid pain relief for critically ill patients, as the onset of action is almost immediate with 100% bioavailability of the drug. Patient-controlled analgesia is only suitable for the extubated and co-operative recovery or intensive care patient.

Intramuscular injection

Intramuscular injections are sometimes administered for postoperative pain relief. However, while this route may have the advantage of being familiar, low tech and low cost, it may be too rigid a prescription and not provide effective analgesia. Absorption is variable depending on peripheral perfusion, and pain and irritation are common at the injection site (Anstey et al 2002). This route is rarely used.

Subcutaneous route

Subcutaneous analgesia may be administered as a single injection or infusion into the fatty tissue beneath the skin. This method is dependent on the fat-solubility of the drug and is dependent on peripheral perfusion. This route may be ineffective or unpredictable in patients with low cardiac output states or on high dose vasoconstrictors. It may provide effective analgesia but can cause pain and discomfort at the injection site (Munden 2003).

Nasogastric

The nasogastric tube may be used as a route for administering analgesia in the form of an elixir or crushed tablets. Absorption is variable depending on gut motility, which can be partly assessed by absorption of nasogastric feed and the volume of nasogastric aspirate. Bioavailability is always reduced in comparison with the intravenous route. It is unsuitable if a patient is nil by mouth or receiving total parenteral nutrition. This route is rarely used in the recovery room.

Rectal route

Rectal administration of analgesia is possible when other routes are not an option. This route of administration avoids first pass metabolism but can have a slow onset of action and variable absorption. The degree of analgesia may also depend on how high in the rectum the suppositories are placed. Patient consent should be sought prior to the administration of medicines via the rectal route therefore this may not be a suitable route in the immediate postoperative period unless prior consent has been gained.

Epidural

Epidural analgesia may provide excellent pain relief but is not routinely administered to mechanically ventilated and unconscious patients partly due to the need for regular assessment of motor block and dermatomal level to prevent serious complications, such as hypotension, respiratory and cardiac depression (Cox 2001). Epidural analgesia is contraindicated in patients with sepsis, coagulopathies or low platelets. Epidural analgesia may be useful for pain relief and respiratory weaning in trauma patients, for example in patients with fractured ribs.

Precautions

Raised arterial pCO_2

Practitioners caring for the critically ill may have concerns when administering opioids in patients who exhibit raised arteriall pCO_2 on their blood gas analysis. This may be due to a direct effect of the

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opioids on the mu receptors in the pons and medulla which alters the rate, depth and rhythm of respirations resulting in CO_2 retention (Stannard & Booth 2004). Raised arterial pCO_2 is obviously not a problem in patients who are mechanically ventilated. However, opioid-induced respiratory depression should be considered if the arterial pCO_2 level is elevated in patients who are weaning or extubated, regardless of the pO_2 level. This should be assessed in the context of sedation score and information concerning underlying lung function. The opioid infusion rate should then be reduced or stopped and alternative analgesia such as intravenous paracetamol should be considered.

Renal impairment

Patients with renal impairment present particular problems when prescribing analgesic and sedation regimes in the recovery or intensive care unit, due to impaired excretion and metabolism of drugs that are handled by the kidney. This can lead to accumulation of analgesics and sedatives, with consequent side effects. Drugs which themselves can cause renal impairment must be avoided to prevent further deterioration in renal function. The pharmacokinetics and metabolism of the individual drugs influence the selection of safe analgesics and appropriate drug dosage adjustments. A prolonged half-life of the drug or its active metabolites leads to increased side effects such as sedation and respiratory depression. This will delay weaning from mechanical ventilation, impair neurological assessment, and prevent regular sedation holds. This will inevitably lead to increased complications of immobility and ventilation and protracted intensive care unit stays.

In general, medicines which are highly protein bound have a molecular weight (greater than 26,000 daltons) or a large volume of distribution (greater than 2L/Kg) are poorly cleared by haemofiltration. Water-soluble drugs, which are renally excreted, are more readily removed. The clearance achieved by haemofiltration is approximately 16ml/min as opposed to a normal clearance of 120ml/min in a healthy individual, with normal renal function (Beresford 2002).

Hepatic impairment

Most analgesics have reduced clearance in patients with hepatic impairment but the significance of this has not been studied in depth in the clinical setting. According to ANZCA (2005), the available data suggests the following:

- Paracetamol may accumulate unpredictably and lead to hepatic necrosis. There should be regular monitoring of hepatic function in patients with mild hepatic cirrhosis and should be avoided in patients with greater degrees of hepatic impairment.
- Tramadol may need to be given at lower doses.
- Methadone is contraindicated in severe liver disease due to the potential for greatly prolonged clearance.
- Local anaesthetics should be administered with caution and in decreased doses (BNF 2008).
- Morhine is metabolised by glucronidation in the liver and should therefore be used cautiosly in reduced dosage in sever liver dysfunction.

Conclusions

Effective analgesia is a basic requirement of patients in hospital. This extends to patients in the recovery or intensive care unit. The complexity of their conditions and treatment makes provision of good, safe analgesia more challenging, but is achievable with an understanding of the underlying condition, careful pain assessment and appropriate selection of suitable techniques and medicines, which will have minimal side effects and impact on underlying pathology. Pain assessment is more difficult in these patients, and conventional pain assessment tools, not always appropriate. In the selection of appropriate drugs, multiple drug and patient factors have to be taken into consideration. Equally, not all routes of administration will be suitable in patients with systems failure. Failure of gastrointestinal function and gut absorption, precludes the oral or naso-gastric route, for example. The presence of renal or hepatic failure makes the pharmacokinetics and pharmacodynamics of the drugs more unpredictable. A multi-modal approach to analgesia will therefore minimise the total individual dose of a drug and limit side effects. Renal and hepatic function must be closely monitored – deteriorating function necessitating review and changes to drugs and doses in the analgesic regimen.

Drugs with short half-lives, which do not rely on hepatic or renal function for metabolism, allow rapid reversal of analgesia and sedation (for example, remifentanil). This facilitates frequent neurological assessment, which is essential in intensive care medicine. Procedural pain in recovery or on the intensive care unit is frequently not considered, and therefore analgesia not given in anticipation of patient discomfort, during line insertion, suctioning, and so on. Staff must understand that sedation does not equate with analgesia. The provision of good analgesia will aid respiratory function and weaning, patient mobilisation, prevent thromobembolic complications, and facilitate rapid recovery and discharge to the ward environment. This will inevitably decrease complications of immobility and a protracted hospital stay. ■

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Staff must understand that sedation does not equate with analgesia

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