Opioid and non-opioid analgesics in the ICU

Opioid analgesics
Opioid analgesic drugs remain the mainstay of pain relief in the Critical Care Unit. Abnormal GI function in the critically ill consequently makes enteral administration undesirable. IV administration remains the mainstay. Pharmacokinetic considerations consequent upon organ dysfunction leading to altered absorption, distribution and metabolism usually play the most important role in the choice of agent.

Most analgesics used on the ICU are metabolized via phase I or II pathways, and they are generally effectively metabolized in all but those with severe liver dysfunction. Metabolism is generally affected by liver blood flow rather than hepatocyte function. Opioids exert their analgesic action by binding to the opioid receptors at both spinal and supraspinal sites. Unwanted effects include bradycardia, miosis, hypothermia, nausea, urinary retention, respiratory depression and constipation.

Route of administration
The IV route is the most reliable way of delivering opioids in the critically ill. Extradural opioids have been used, often in combination with local anaesthetics; inhalational and transmucosal opioids are only rarely used. Patient-controlled modes of administration require a fully conscious and orientated patient, and are therefore only of limited value in the CCU.

Choice of drug
The most commonly used opioids are morphine, fentanyl, alfentanil and remifentanil.

Morphine
Morphine is the most often prescribed agent because of its low cost, excellent analgesic efficacy and euphoric effects. It has a peak effect within 20min, and duration of action between 2 and 7h. It has low lipid solubility and volume of distribution, and its duration of action is determined by hepatic metabolism. It is metabolized by the liver to the water-soluble morphine-6-glucuronide and morphine-3-glucuronide, which are then renally excreted. Morphine-6-glucuronide is 2–800 times analgesically more potent than morphine and accumulates in renal dysfunction. This can lead to unwanted prolonged sedation and respiratory depression. Morphine-3-glucuronide is not analgesically active.

Fentanyl, alfentanil and remifentanil
Fentanyl is a synthetic opioid; it is the preferred analgesic agent for critically ill patients with haemodynamic instability and for patients manifesting symptoms of histamine release with morphine or morphine allergy. Fentanyl is 50–100 times more potent than morphine; it has extremely low bioavailability and therefore can be given by any route other than the GI tract. It is extremely lipid soluble and has an onset of action within 30s, with a peak effect in 5–15min. It has a short half-life of 30–60min following redistribution, but accumulation in peripheral compartments can increase the half-life to 9–16h. Fentanyl is metabolized in the liver to pharmacologically inactive metabolites, which are renally excreted. In critically ill patients with renal failure there is an increase in the volume of distribution and half-life of fentanyl. Fentanyl has minimal cardiovascular effects compared with morphine. Following a long infusion of fentanyl, accumulation may cause prolonged respiratory depression.

Alfentanil is a phenylpiperidine synthetic opioid. It has similar pharmacodynamic properties to the other newer opioids, but it shows considerable variability in its pharmacokinetic profile from patient to patient. Interindividual variability in alfentanil clearance is likely to result from differences in hepatic P450-3A4 expression and to P450-3A4-related drug interactions.

Remifentanil has an extremely short context-sensitive half-life and is independent of hepatic and renal function. In the cardiac- and neuro-ICU setting, remifentanil’s short half-life is especially desirable. It allows good neurological assessment when required, profound haemodynamic stability and early extubation after bypass surgery. One study suggests that the intraoperative use might even reduce the need for a post-operative ICU stay after major abdominal surgery.

Table 13.1.1 outlines commonly used regimes for opioid infusion in Critical Care Units.

Table 13.1.1 Infusion rates for commonly used opioids in critical care

<table>
<thead>
<tr>
<th>Drug</th>
<th>MEAC ng/ml</th>
<th>$t_{1/2}$ terminal (min)</th>
<th>Dose mcg/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>50–100</td>
<td>90</td>
<td>30–60</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1–3</td>
<td>185</td>
<td>1–5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.2–0.5</td>
<td>160–210</td>
<td>0.2–3.0</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>n/a</td>
<td>10–20</td>
<td>30–60</td>
</tr>
<tr>
<td>Morphine</td>
<td>10–30</td>
<td>100–180</td>
<td>50–100</td>
</tr>
</tbody>
</table>

MEAC = minimally effective analgesic concentration.

Non-opioid analgesics
Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs have opioid-sparing effects and have both central and peripheral sites of analgesic activity. The use in the critically ill is however controversial. Their metabolism and excretion is dependent on liver and kidney function, both of which pathways are frequently impaired in the ICU patient. NSAIDs increase the prostaglandin-dependent renal blood flow and are associated with an increased gastric ulceration risk. It seems prudent to avoid this class in the critically ill in the absence of any definite gain to be had.

A new class of agents has been developed that selectively inhibit the inducible cyclo-oxygenase enzyme, COX-2. By sparing physiological tissue prostaglandin production while inhibiting the COX-2-related inflammatory processes, these agents are thought to offer the potential of effective analgesia with fewer side effects than previous NSAIDs. They have been shown to be as effective as NSAIDs in the management of post-operative analgesia. Adverse effects on renal blood flow, which are similar those of to conventional NSAIDs, and concerns regarding potential prothrombotic effects of at least some of the COX-2 agents, will limit their use in the critically ill patient.

Ketamine
This IV anaesthetic agent has intense analgesic properties even at subanaesthetic levels, maintaining the airway, and has stimulatory effects on the respiratory and cardiovascular system. It is used in specific painful procedures, particularly in burn patients for dressing changes.
Hallucinations and emergence phenomena can be attenuated by the co-administration of benzodiazepines.

There is furthermore some evidence, that ketamine can be useful in chronic pain states such as central pain, complex regional pain syndrome, fibromyalgia and neuropathic pain. Either alone or in combination with opioids it provides rapid, effective and prolonged analgesia.

**Neuropathic pain agents**

Some patients may be suffering from or develop neuropathic pain. This sort of pain may be difficult to manage with standard analgesics, and consideration should be given to adding in specific drugs for neuropathic pain as outlined in Table 13.1.2. Patients may also have pre-existing neuropathic pain problems; medication should be continued where possible.

**Table 13.1.2 Adjuvant therapies for pain in critical care.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose mg</th>
<th>Neuropathic pain</th>
<th>Sleep</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic</td>
<td>20–100</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>antidepresants</td>
<td>nocete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100–900</td>
<td>++</td>
<td>+</td>
<td>+?</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25–300</td>
<td>++</td>
<td>+</td>
<td>+?</td>
</tr>
</tbody>
</table>

PTSD = post-traumatic stress disorder.

**Adjuvant therapies**

Especially in patients with features of chronic pain or altered sleep patterns, tricyclic antidepressants have been used extensively. There might be a rationale for using these drugs in the medium- to long-stay patient where a constellation of pain, anxiety and depression co-exists, possibly along with a disturbed sleep pattern. There is evidence that the usage of tricyclics, and possibly some of the drugs used to treat neuropathic pain, may reduce the development of post-traumatic stress disorder (PTSD) in ICU survivors.

**Alternative therapies**

No evidence exits to support the use of alternative therapies in the critically ill. In the absence of any untoward effects, however, the use of transcutaneous electrical nerve stimulation (TENS), acupuncture, aromatherapy, etc., should not be withheld. Anecdotal evidence suggests a benefit from acupuncture in neuropathic pain, and reduced sedative and analgesic requirements following aromatherapy.

**Summary**

Opioids are the most commonly used analgesic agents, often giving in combination with sedative drugs. There is no doubt that this method is effective and cheap, and staff have a wealth of experience in its use. However, such regimes do not provide satisfactory pain relief in all patients.

What is needed to avoid patients experiencing pain while in the ICU is individualized, goal-directed analgesic regimes in their own right, not as a side effect of sedation. In concert with analgesia, anxiety, the physical environment and the patient’s sleeping pattern need to be considered. Adherence to a clear protocol may be as important as choice of medication.

**Further reading**


