Sedation and analgesia

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Sedation is a process of soothing\(^1\). The concept of the ideal level of sedation is controversial and has changed over the last decade. A shift from deep sedation, often enhanced by muscle relaxants that completely detaches the patient from their environment, to light sedation rendering the patient sleepy but easily arousable has been widely accepted\(^2\). This change in attitude has been brought about by sophisticated modes of ventilation allowing the ventilator to synchronise with the patient’s own breathing pattern. In addition, the increasingly recognised adverse effects of over-sedation have contributed to the reduction in the depth of sedation\(^3\).

Aims of sedation

The main aim of sedation is to relieve anxiety, discomfort, minimize pain, facilitate treatment and nursing care. Nocturnal sedation may reduce sleep deprivation. Occasionally amnesia, respiratory depression and anti-tussive effects are needed\(^4\). This is because there are a number of factors contributing to physical and psychological distress in critically ill patients as summarised in Table 1.

Goals of sedation differ in each patient and change during the disease process depending upon whether the disease is improving or worsening.

Table 1 Factors contributing to physical and psychological distress in critically ill patients

- Sterile, frightening ICU environment
- Pain related to trauma, surgery, organ disease
- Invasive procedures
- Paralysis with muscle relaxants without adequate sedation
- Modes of ventilation not synchronised with physiological breathing patterns
- Tracheal Intubation
- Inability to communicate
- ICU psychosis, depression, depersonalisation
- Sleep deprivation
- Fear, anxiety concerning welfare of relatives, and their own prognosis
- Thirst
- Feeling of dependence and loss of control
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Table 2  Some indications for deep sedation and therapeutic paralysis

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Raised intracranial pressure to</td>
</tr>
<tr>
<td>• reduce cerebral metabolic rate</td>
</tr>
<tr>
<td>• avoid straining coughing</td>
</tr>
<tr>
<td>• reduce intracranial pressure</td>
</tr>
<tr>
<td>• Poor pulmonary compliance to tolerate unusual forms of ventilation such as reversed ratio</td>
</tr>
<tr>
<td>• Critical oxygenation to</td>
</tr>
<tr>
<td>• reduce oxygen consumption</td>
</tr>
<tr>
<td>• reduce the risk of difficulty in synchronising with the ventilator and so worsen oxygenation</td>
</tr>
<tr>
<td>• Tetanus</td>
</tr>
<tr>
<td>• Fits – difficult to stop even with large doses of anticonvulsants</td>
</tr>
<tr>
<td>• Hyperpyrexia – to reduce the work of hyperventilation and further heat generation.</td>
</tr>
</tbody>
</table>

There are still a few indications for a deep sedation including therapeutic paralysis. These are summarised in Table 2.

There are numerous ways to help a patient need less or no drugs to tolerate intensive care. Talking to the patient along with constant reassurance, a pleasant environment, sufficient night sedation, all help. Attentive nursing care by avoiding pressure sores and mouth care reducing the perception of thirst are also extremely important.

Skilful pain management and additional analgesia to cover painful interventions need to be given. Mechanical ventilation is best tolerated if assisted modes are used that synchronise with the patient’s respiration such as BIPAP (biphasic positive airway pressure). For long-term ventilation, tracheostomy is a more comfortable alternative to orotracheal intubation. Therapeutic paralysis must always be complemented by sufficient sedation to prevent the patient being awake and unable to move. When patients are questioned after leaving the ICU they remember that anxiety and pain are amongst the most distressing factors.

Evidence-based medicine

Sedation and analgesia should be based on scientific information, but this is often difficult. The heterogeneity of the ICU population makes it difficult to identify homogenous groups. Despite profound changes of pharmacodynamics and pharmacokinetics in the critically ill patient, most data about the effect of drugs have been extrapolated from healthy individuals or patients in a stable part of their chronic disease. This has led to inappropriate use of some drugs, for example muscle relaxants in the acutely ill, unstable patient. Because these difficulties create a lack of consistent statistical data, individualised drug therapy with careful monitoring of the clinical response is still the most common practice.
Pharmacodynamics and pharmacokinetics in the critically ill

Multiple drug therapy is universal in the critically ill patient making unexpected drug interactions likely. Most drugs are given intravenously and have a narrow therapeutic index. Drugs also have an effect on organ dysfunction. Also the pharmacokinetics and pharmacodynamics of the drugs are changed by the underlying disease. Interventions such as haemodialysis, mechanical ventilation and plasmapheresis further influence drug disposition. All those unknown variables complicate drug administration including analgesics and sedatives. As a result, the patient's clinical response is often unpredictable with a high interindividual variability. Furthermore, variability in the same patient may change during their stay in the ICU.

Pharmacokinetics and pharmacodynamics in organ system failure

Hepatic failure

The liver is the principal organ for drug metabolism, although extrahepatic sites of drug metabolism exist. The significance of these extrahepatic sites varies depending on the drug. For example, they contribute about 10% for midazolam, but can replace the liver entirely for remifentanil. Depending on the nature of liver failure, different functions will be affected. In acute liver failure, all main liver functions fail within a short interval including synthesis, storage, metabolism and biliary excretion. However, in the stable phase of chronic liver disease, only one function may be affected. For example, in cholestatic disease, the excretory function fails, resulting in an increase in the plasma concentration of conjugated metabolites.

The central nervous system receptor sensitivity to sedative agents is enhanced in patients with liver disease. Table 3 shows some of the changes seen in liver failure.

Table 3 Effects of liver failure on the pharmacokinetics of drugs

<table>
<thead>
<tr>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Volume of distribution</td>
</tr>
<tr>
<td>* fluid compartment capacity (ascites, circulatory volume)</td>
</tr>
<tr>
<td>• Free drug fraction</td>
</tr>
<tr>
<td>• Accumulated metabolites and</td>
</tr>
<tr>
<td>• Structurally abnormal protein binding sites</td>
</tr>
<tr>
<td>• Sensitivity of some receptors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatic clearance</td>
</tr>
<tr>
<td>* reduced liver blood flow</td>
</tr>
<tr>
<td>* reduced extraction ratio</td>
</tr>
</tbody>
</table>
Sedation and analgesia

The liver is able to compensate for parenchymal damage of up to 90%. More severe liver failure poses several problems. The frequency of drug administration and the infusion rates usually need to be reduced and carefully titrated. Drugs undergoing extra hepatic metabolism (such as propofol and remifentanil) may be preferable to those with no alternative sites of metabolism

Renal failure

The kidneys are extremely susceptible to underperfusion. Patients with sepsis and multiple organ dysfunction are in danger of developing acute renal failure. Early recognition of high risk patients and institution of preventive measurements are paramount. Furthermore, once renal failure has developed the accompanying uraemic encephalopathy exaggerates sedative and analgesic effects.

When renal failure has developed, the clearance of drugs removed by the kidney is reduced prolonging their effect. Renal elimination of active metabolites, for example morphine\textsuperscript{18,19} and midazolam\textsuperscript{20}, also stops. Drugs mainly dependent on glomerular filtration accumulate. Creatinine clearance can be misleading as a guide for adjustment of drug doses, since critically ill patients have an altered creatinine metabolism\textsuperscript{9}.

Haemodialysis and haemofiltration may change the clearance of drugs. This may vary according to mode of dialysis and type of membrane used\textsuperscript{10,11}. Agents transformed to active metabolites, such as diazepam, morphine, pethidine, should only be used with caution. Preferable are short-acting drugs metabolized to inactive, non-toxic metabolites. Propofol is a satisfactory sedative and alfentanil a useful analgesic agent\textsuperscript{1}. Remifentanil may be a useful agent once it has been evaluated\textsuperscript{21}.

Multiple organ dysfunction syndrome

Extensive tissue damage can trigger the systemic inflammatory response syndrome releasing mediators of inflammation. Alterations in haemodynamics, microcirculation and oxygen utilisation occur. Those changes can cause any organ of the body to fail and multiple organ dysfunction syndrome (MODS) follows\textsuperscript{22}.

Many critically ill patients suffer from MODS. Systemic inflammatory response causes an increase in capillary permeability and total body water. Hepatic metabolism and renal excretion of drugs is reduced, risking accumulation while an encephalopathy increases sensitivity. During convalescence, the reverse mechanisms occur\textsuperscript{23}.
Intensive care medicine

**Insult**
- infectious (sepsis)
- non-infectious
  (extensive tissue trauma, ischemia, hypoxia)

**Systemic Inflammatory response syndrome (SIRS)**
- systemic release of mediators

**Haemodynamic changes**
- vasodilatation
- myocardial depression
- redistribution of flow

**Microvascular changes**
- endothelial damage
- microemboli
- AV shunting

**Impaired O₂ utilisation**
- Cellular Hypoxia
dysfunction of any organ

**BRAIN**
- Encephalopathy
  - uraemic
  - hepatic
  - hypoxic
  - CNS receptor sensitivity
to sedatives and analgesics

**CVS**
- redistribution of cardiac output to heart and brain
  - Volume of Distribution initially
  - drug concentration in heart/brain
- Increased capillary permeability
  - Volume of Distribution
  - body water
  - plasma concentration of drugs
- **myocardial depression**
  - cardiogenic shock with hypoperfusion of:
    - gut
    - kidneys
    - adrenal glands
    - brain
    - heart
    - liver
    - any other organ

**KIDNEY**
- Acute Tubular Necrosis
  Need for haemofiltration
  - renal clearance of drugs or their active and inactive metabolites

**LIVER**
- Hypoperfusion
  - hepatic clearance
  - accumulation of drugs metabolised by the liver
  - Volume of Distribution
  - Free drug fraction

**GUT**
- Breakdown of intestinal Integrity
  - No administration of sedatives/analgesics
  - via enteral route

**Drug monitoring**

Drugs with a narrow therapeutic index need careful monitoring. Systemic drug concentration is measured in some drugs and therapeutic and toxic ranges are clearly defined. However, in critical illness, the plasma concentration and concentration at site of action may not correlate. This is especially true for the sedative and analgesic drugs. Many factors may affect their action. Drug levels may be misleading and clinical signs of drug response and toxicity must be actively looked for. The measurement of the plasma concentration is of little value⁹,¹².
Assessing sedation

Regular assessment of the level of sedation should be routine in all ICU patients. It aims to prevent the hazards of over or under sedation which are associated with an increased morbidity and even mortality. There are objective and subjective means of assessing the level of sedation.

Objective means, such as the EEG and evoked potentials, are rarely used. They can be unreliable for distinguishing drug effects from those of disease. Additional equipment and training are needed for meaningful interpretation.

Table 4  The Ramsay sedation scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient awake, anxious or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Patient awake, cooperative, orientated and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Patient awake, responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Patient asleep, brisk response to light glabellar tap</td>
</tr>
<tr>
<td>5</td>
<td>Patient asleep, sluggish response to light glabellar</td>
</tr>
<tr>
<td>6</td>
<td>Patient asleep, no response to light glabellar tap</td>
</tr>
</tbody>
</table>

The Ramsay sedation scale (Table 4), an ordinal scaling system describes the level of consciousness. The assessment is subjective. It is not a scoring system, since moving from level 2 to 4, for example, is not a doubling of sedation and does not include information about the quality of sedation. Levels 2-4 of the Ramsay scale are currently thought to represent the ideal level of sedation.

We use a similar approach but add further information to improve on its limitations such as information about the state of sleep and paralysis (Table 5). It is worthwhile emphasising the additional use of muscle relaxants since adequate sedation must be guaranteed. Recording the exact number of hours slept will facilitate the diagnosis of sleep deprivation and treatment can be instituted. Assessment of pain relief and tolerance to ventilation are added as well.

Scoring systems giving an index of quality of sedation are less subjective and more reproducible. One example is illustrated in Table 6.

Table 5  The Addenbrooke’s sedation scale

<table>
<thead>
<tr>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitated</td>
</tr>
<tr>
<td>Awake</td>
</tr>
<tr>
<td>Roused by voice</td>
</tr>
<tr>
<td>Roused by tracheal suction</td>
</tr>
<tr>
<td>Unrousable by tracheal suction</td>
</tr>
<tr>
<td>Paralysed</td>
</tr>
<tr>
<td>Asleep</td>
</tr>
<tr>
<td>Pain (yes/no)</td>
</tr>
<tr>
<td>Tolerance to ventilation (yes/no)</td>
</tr>
</tbody>
</table>
### Table 6 A scoring system to measure depth of sedation

<table>
<thead>
<tr>
<th>Response</th>
<th>Level of response</th>
<th>Sedation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes open</td>
<td>Spontaneously</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>Spontaneously strong</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Spontaneously weak</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>On suction only</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Motor response</td>
<td>Obey command</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Purposeful movements</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Non-purposeful movements</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Respiration</td>
<td>Extubated</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Spontaneous, intubated</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Triggering the ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Breathing against ventilator</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No respiratory efforts</td>
<td>1</td>
</tr>
<tr>
<td>Grades of sedation</td>
<td>Awake</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Asleep</td>
<td>14 - 16</td>
</tr>
<tr>
<td></td>
<td>Light sedation</td>
<td>11 - 13</td>
</tr>
<tr>
<td></td>
<td>Moderate sedation</td>
<td>8 - 10</td>
</tr>
<tr>
<td></td>
<td>Deep sedation</td>
<td>5 - 7</td>
</tr>
<tr>
<td></td>
<td>Anaesthetized</td>
<td>4</td>
</tr>
</tbody>
</table>

The number of points in each category is added giving an estimated grade of sedation and sedation can be adjusted accordingly to the desired level.

### Choice of sedative agents

No drug approaches the ideal properties of a satisfactory sedative regimen. The route and mode of administration must be tailored to each individual patient. Drugs that are principally analgesic, mainly opioids, or principally hypnotics are used. Amongst the hypnotics, propofol and benzodiazepines are common. Inhalational anaesthetics, such as isoflurane, are a rarely used alternative.

### Route and mode of administration

The enteral route is best avoided. The gastrointestinal tract commonly fails in the critically ill patient and is unpredictable. Similarly, the time of onset or a drug concentration when a drug is given subcutaneously or intramuscularly is dependent on blood flow at the site of injection and is also unreliable.
The intravenous route is preferred. Although differences between healthy and critically ill patients exist, it is the most predictable option with the shortest onset time. In the ICU it is easy to use. Several ways of using the intravenous route are available for sedative and analgesic drugs. These include intermittent bolus injection, continuous i.v. infusion, nurse controlled analgesia and patient controlled analgesia once the patient is able to co-operate.

**Pain relief in the ICU**

Patients on the ICU commonly experience pain related to tissue damage caused by traumatic injury, surgery or visceral disease. Adequate pain relief is not only humanitarian, but reduces morbidity. The adverse effects of pain are shown in Table 7 and include an exaggerated sympathetic and neuroendocrine response. The excretion of thyroxine, catecholamines, glycocorticoids, aldosterone, angiotensin, and growth hormone is increased. A dominant sympathetic tone causes increased cardiac work and myocardial oxygen consumption. Thoracic and abdominal wounds reduce respiratory excursions and splinting of the diaphragm and abdominal muscles. The functional residual capacity (FRC) is low and alveolar ventilation poor. Coughing is cautious because of the pain, resulting in retention of secretions, atelectases and infection. Respiratory failure follows. Immobility due to pain encourages deep venous thrombosis and intestinal stasis. Sleep deprivation leads to the development of ICU psychosis.

**The characteristics of pain**

The unpleasant emotional and sensory character of pain is associated with actual or potential tissue damage. Pain perception is complex and

<table>
<thead>
<tr>
<th><strong>Table 7</strong> Adverse effect of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroendocrine response</strong></td>
</tr>
<tr>
<td>• ↑Thyroxine, glucocorticoids, aldosterone, angiotensin, growth hormone</td>
</tr>
<tr>
<td><strong>Sympatho-adrenal response</strong></td>
</tr>
<tr>
<td>• ↑Catecholamines</td>
</tr>
<tr>
<td>• ↑Cardiac work, ↓myocardial O₂ consumption</td>
</tr>
<tr>
<td><strong>Respiratory impairment</strong></td>
</tr>
<tr>
<td>• Ineffective cough, diaphragmatic splinting, retention of secretions, infection, ↓FRC, atelectases, poor alveolar ventilation (especially in thoracic and abdominal wounds)</td>
</tr>
<tr>
<td><strong>Immobilization due to pain</strong></td>
</tr>
<tr>
<td>• ↑Risk of deep venous thrombosis</td>
</tr>
<tr>
<td>• ↑Intestinal stasis</td>
</tr>
<tr>
<td><strong>Sleep deprivation</strong></td>
</tr>
<tr>
<td>• Development of ICU psychosis</td>
</tr>
</tbody>
</table>
affected by the psychological profile, the sociocultural background, insight and motivation, age and anxiety level of the patient. Other aspects of physical discomfort (nausea, vomiting, urinary retention, tracheal tube) and a hostile environment (noise, bright light) aggravate pain

Pain can be visceral or somatic in nature. Visceral pain presents as a dull nagging diffuse background pain. If it is somatic then it is rather well defined, stabbing and severe and often associated with movement.

Acute pain is generally self-limiting, easing off after 3–5 days. However, repeated surgical operations can prolong the duration of severe acute pain. Upper abdominal and thoracic surgery are associated with severe pain while lower abdominal, head and limb surgery causes less severe pain.

Recent developments suggest that neuroplasticity and ‘wind up’ mechanisms transforming acute into chronic pain can be prevented by the accurate use of newer analgesic groups, for example antagonists of nitric oxide synthesis and NMDA receptors. Their usefulness in the ICU setting has yet to be established.

**Analgesia**

Opioids remain the mainstay of analgesia in the critically ill. They act on opioid receptors of which there are several different types. There has been some confusion over the nomenclature in the past. In an attempt to unify opioid receptor classification, the International Union of Pharmacology (IUPHAR) has reclassified opioid receptors as OP₁ (δ), OP₂ (κ) and OP₃ (μ). Note that the σ receptor is no longer considered an opioid receptor. The effects of these receptors are shown in Table 8.

Adverse effects, such as respiratory depression and impaired intestinal activity, can be deleterious to the patient and must be minimized. The cardiovascular system is little affected by opioids, if therapeutic doses

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP₁ (μ)</td>
<td>Supraspinal analgesia</td>
<td>Morphine</td>
<td>Naloxone</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>β-Endorphin</td>
<td>Pentazocine</td>
</tr>
<tr>
<td></td>
<td>Euphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP₂ (δ)</td>
<td>Modulation of μ receptor activity</td>
<td>Leu-enkephalin</td>
<td>Naloxone</td>
</tr>
<tr>
<td></td>
<td>Supraspinal analgesia</td>
<td>β-Endorphin</td>
<td>Met-enkephalin</td>
</tr>
<tr>
<td></td>
<td>?Pentazocine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP₃ (κ)</td>
<td>Spinal analgesia</td>
<td>Dynorphin</td>
<td>Naloxone</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Pentazocine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td>Nalbuphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Butorphanol</td>
<td></td>
</tr>
</tbody>
</table>

Table 8 Opioid receptors, their nomenclature, agonists and antagonists
Sedation and analgesia

**Table 9  Recommended opioid dosage**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incremental i.v. bolus</th>
<th>Patient controlled analgesia system (PCAS)</th>
<th>Continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PCA bolus</td>
<td>Lockout period</td>
</tr>
<tr>
<td>Morphine</td>
<td>2.5 mg</td>
<td>1 mg</td>
<td>5 min</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>1 mg</td>
<td>0.5 mg</td>
<td>5 min</td>
</tr>
<tr>
<td>Pethidine</td>
<td>5-10 mg</td>
<td>10-20 mg</td>
<td>5 min</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-50 μg</td>
<td>10-30 mg</td>
<td>5 min</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>250 μg</td>
<td>Not recommended</td>
<td>0.03-0.3 mg/kg/h</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.5 μg/kg</td>
<td>Not recommended</td>
<td>0.05-0.2 μg/kg/min</td>
</tr>
</tbody>
</table>

...are used. Pruritus, urinary retention, nausea and vomiting and constipation are less obvious in the critically ill and can be treated as required. Tolerance is common, but dependence rarely occurs. Dependence can be triggered if excessive doses are used over a prolonged period and in the absence of pain.

In haemodynamically unstable patients, opioids are best given in small increments at short-time intervals until pain is controlled. The use of patient-controlled analgesia is often limited by the impaired ability of cooperation in critically ill patients. Initially, the nurse can administer the boluses. However, an important safety aspect is lost in nurse-controlled analgesia since an over-sedated patient will be unable to continue self-administration of pain relief, but a nurse can continue ‘pressing the button’. Therefore, the need for repeated pain assessment cannot be overemphasized. Recommended opioid dosages are given in Table 9.

**Morphine**

Morphine remains the standard opiate. It is effective and cheap. The onset time is slow at 20 min owing to a low lipid solubility. More than 90% is metabolised in the liver. The main metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G may be inactive or even antianalgesic. However, M6G is at least 20 times more potent with a longer duration of action than morphine. In renal failure, M6G accumulates and this can be the cause of prolonged coma.

**Phenyl piperidines**

The group of opioids comprises pethidine, fentanyl, alfentanil, sufentanil and remifentanil. They are synthetic substances; potent μ-receptor agonists like morphine but with quite different pharmacokinetics. The main metabolite of pethidine has the potential to cause central nervous system excitation and is unsuitable for long-term use in patients with renal failure.
Fentanyl
Fentanyl has a 100-fold potency of morphine owing to a high receptor affinity. It is very lipid soluble resulting in a rapid onset time of 3 min, because it diffuses quickly into the central nervous system. The effect diminishes after 20 min owing to redistribution into inactive peripheral tissues. Once all tissues are saturated it lasts longer than morphine because ending of its effects depends on metabolism. Fentanyl is metabolised in the liver by N-demethylation to norfentanyl which undergoes urinary excretion. As with morphine, the parent substance accumulates in hepatic failure while its metabolites accumulate in renal failure with the potential to cause an acute toxic delirium and a reduced analgesic effect. Long-term administration, especially as continuous infusion, may be cumulative. Fentanyl occasionally produces increased muscle rigidity and seizure activity. It releases less histamine than morphine.

Alfentanil
Alfentanil has an onset time of only 1 min, equal to one arm-brain circulation time, despite being less lipid soluble than fentanyl. The explanation is its low pKa with an unionised fraction of 90% (fentanyl 10%) at physiological pH. Its initial effect lasts 15 min because of its fast redistribution. Almost all (99%) is metabolised in the liver to inactive metabolites. Severe hepatic failure can prolong this effect, but it is currently the drug of choice in renal impairment.

Remifentanil
Remifentanil is a relatively new agent and has not been widely used for sedation. Its ester linkage makes it susceptible to metabolism by non-specific esterases, resulting in a very short duration of action of 2–3 min. The non-saturable esterases provide rapid and predictable elimination independent of renal or hepatic metabolism. Onset time is about 30 s. Its main drawback is cost. Side effects, especially after bolus injections, can be marked but are usually short-lived. Respiratory depression, apnea, hypotension, bradycardia and muscle rigidity are commonly observed. Remifentanil can provide fast and short acting sedation with respiratory suppression and analgesia. It allows fast emergence, early central nervous system assessment and facilitates early tracheal extubation after major surgery. These characteristics might be desirable in selected patients, for example in patients with an encephalopathy.

Tramadol
Tramadol is a μ-receptor agonist producing analgesia. It releases serotonin and inhibits serotonin and noradrenaline uptake. This causes a monoaminergic effect with central nervous system stimulation, increased blood
pressure and heart rate. Nausea and vomiting can be profound. It is an alternative to opioid analgesia especially if sedation and cardiovascular instability are undesirable. Tramadol is given i.m. or i.v. in incremental boluses of 50 mg at 10–20 min intervals until pain is relieved. Maintenance is achieved with 50–100 mg every 4–6 h.

Non-steroidal anti-inflammatory agents

These act by inhibiting the enzyme cyclo-oxygenase, in turn reducing prostaglandin synthesis and producing an anti-inflammatory, anti-pyretic and analgesic effect. There are two types of cyclo-oxygenase. Type 1 is a constitutive enzyme and is always present and involved in homeostasis, vascular response and gastrointestinal protection. Serious side effects are attributed to its inhibition. Type 2 is an inducible enzyme in inflammatory cells and if blocked selectively produce antipyretic, anti-inflammatory and analgesic effects. Adverse reactions are minimal. Unfortunately all currently available NSAIDs inhibit Type 1 as well as Type 2 cyclo-oxygenase to various degrees. Despite their good therapeutic qualities, adverse effects like gastrointestinal bleeding, bronchospasm, coagulopathy, renal toxicity and bone marrow suppression limit their use in critically ill patients. In some patients, NSAIDs can be given enterally. Ketorolac and tenoxicam are licensed for i.v. administration.

NSAIDs also exert an analgesic effect if given experimentally intrathecally. Its mechanism of action may not just be inhibition of prostaglandin synthesis but they may also affect the NMDA receptor channel complex. They should not be given to patients by this route yet, except in studies.

Local anaesthetics

For regional anaesthesia, the amide local anaesthetics, bupivacaine and lignocaine, are mainly used. While lignocaine has a short onset time with a duration of 1–2 h the onset time of bupivacaine is longer, up to 30 min and its duration of effect 3–6 h. Systemic toxicity with neurological and cardiovascular complications can occur if the maximum safe doses are exceeded (2 mg/kg of plain bupivacaine and 4 mg/kg of plain lignocaine, 4-hourly). Potentially toxic concentrations may be seen in the critically ill even if less than the maximum doses are given.

The extent of systemic absorption depends on the site of administration. Dangerous serum concentrations can be reached in critically ill patients with multiple organ dysfunction where hepatic and renal failure, changed plasma protein levels and volumes of distribution are common.
Epidural analgesia

Epidural analgesia is the most effective form of analgesia for postoperative pain relief or after chest trauma. Unfortunately, in some critically ill patients, epidural analgesia is contra-indicated because of sepsis and coagulopathy. Other risks include infection of the spinal cord, epidural catheters should normally be removed after 72 h to reduce this. Unfortunately, the episode of critical illness often lasts longer. Performing regional techniques requires a co-operative, awake, patient to reduce the danger of spinal cord damage, this can be lacking in a confused patient suffering pain.

Complications with local anaesthetics differ from those of opioids. Postural hypotension secondary to sympathetic blockade and motor-weakness are major setbacks. To minimise these side effects, the epidural catheter should be placed near to the centre of the painful area reducing the required local anaesthetic dose. If opioids are added, a synergistic analgesic effect reduces requirements further. The newer agent ropivacaine, a bupivacaine derivative, provides anaesthesia with less profound motor-block.

Epidural opioids give pain relief with little postural hypotension. Less opioid is needed than the usual intravenous doses. The effect tends to be longer-acting because of the direct action on opioid receptors in the posterior horn of the spinal cord. Patients are more alert and easier to mobilise. More lipid soluble agents such as diamorphine, fentanyl, alfentanil or sufentanil are associated with reduced cephalad diffusion. However, the expected gain of a minimized risk of respiratory depression is outweighed by the impaired carbon dioxide response of those drugs. Two phases of respiratory depression are seen with epidural opioids. Early respiratory depression within 1 h appears because of systemic absorption. Delayed respiratory depression occurs within 7–24 h due to cephalad spread, especially with less lipid soluble opioids such as morphine. After stopping of epidural morphine or diamorphine, a period of close monitoring is recommended. Such close prolonged monitoring does not seem to be needed after epidural fentanyl, alfentanil or sufentanil.

Local anaesthetic agents with or without opioid supplementation can be given as a continuous infusion or in incremental injection either as patient controlled analgesia or by the patient's attendants. The main advantage of continuous infusion is the greater cardiovascular stability. A recommended solution is 0.1% bupivacaine with 2 μg/ml fentanyl at a rate of 0–10 ml/h. If necessary, the local anaesthetic concentration can be increased to 0.25% or different opioids can be added.
Other regional techniques

If selected carefully, most known regional techniques can occasionally be of use in the critically ill. Intercostal nerve blocks, the placement of interpleural catheters and peripheral limb blocks, all have been performed successfully in these patients.

Sedation

Although the relief of pain is of paramount importance, some patients will need more. There may be the need for anxiolysis, amnesia and hypnosis for example. Other drugs may be used for this as indicated below.

Benzodiazepines

Benzodiazepines are commonly used drugs for sedation in the critically ill. They bind specifically to the $\gamma$-aminobutyric acid complex (GABA) enhancing inhibitory neuronal transmission. The hypnotic, anxiolytic and muscle relaxant effects are beneficial to patients needing mechanical ventilation. The amnesia is of benefit to some. The anticonvulsant effect is exploited in the treatment of fits. Mild physical and psychological dependence may occur and withdrawal causes restlessness and disturbances of natural sleeping pattern$^{1,4,12,24}$.

As with most sedative agents, benzodiazepines exert cardiovascular and respiratory depression especially if used in excessive doses. In therapeutic doses, these effects are minimal. If weaning off mechanical ventilation after long-term use of benzodiazepines, they should be stopped well before. Failure to do so may result in difficulty in weaning because of their prolonged effect. Respiratory depression reduces carbon dioxide response and muscle relaxation reduces respiratory muscle activity.

Midazolam

Midazolam has gained great popularity in the ICU. It is the shortest acting benzodiazepine available. As a water soluble imidazo-benzodiazepine it can be given into a peripheral vein without irritation. Metabolism occurs in the liver by hydroxylation to mostly 1-hydroxy-midazolam which has 10% of the activity of midazolam and is shorter acting.

Accumulation occurs in patients with liver failure. Occasionally midazolam reaches a ceiling effect where further increase in dosage does not approach the desired clinical effect$^{4,12}$. The 1-hydroxy-glucuronide accumulates in renal failure and can cause coma$^{20}$.
Diazepam
Diazepam has been superseded by midazolam in its use for sedation on ICU. It has a longer onset time and some preparations cause thrombophlebitis if given peripherally. It has a long duration of actions and produces several active metabolites, some with a longer duration of action. Desmethyl-diazepam the longer acting metabolite has a half-life exceeding 90 h. Accumulation is a significant risk.

Lorazepam
Lorazepam has been to sedate critically ill patients. However, large amounts may result in solvent (propylene glycol) toxicity.

Anaesthetic drugs

Propofol
Propofol (2,6-di-isopropylphenol) enjoys widespread use for continuous sedation. Introduced in 1986, it is an intravenous anaesthetic induction agent it was soon found that in reduced doses it produces satisfactory sedation. Emergence is fast and without a hangover effect. Propofol is rapidly metabolized with a clearance that exceeds hepatic blood flow suggesting extra hepatic metabolism. The metabolites are inactive, mostly glucuronide and sulphate conjugates. Accumulation is not a concern even in patients with liver or renal failure.

Its haemodynamic and respiratory depressant effect, particularly when large amounts are used, may limit its use. Profound reduction of the systemic vascular resistance and a slight reduction in myocardial contractility without an adequate reflex tachycardia can cause the blood pressure to decrease by up to 40% [45]. Prolonged apnoeic periods can occur.

Its use in children as continuous infusion is not recommended because of the toxicity of its solvent if given in overdose. Propofol is lipid soluble and needs to be formulated as a 1% solution in an aqueous emulsion of 10% soya bean oil with egg phosphatides. This solvent has resulted in toxicity when given in large amounts. Prolonged infusion will increase serum triglyceride and cholesterol concentration, pose problems of fluid overload (mainly if used as a 1% formulation) and costs approximately £100 per day. Its use should be restricted for short-term ventilation or when weaning off the ventilator is imminent.

Ketamine
Ketamine is a phencyclidine derivative acting on NMDA receptors where it inhibits the excitatory effect of glutamate. Beside the sedative
effect, it also has analgesic and bronchodilator properties. Less desirable effects include dissociative anaesthesia, central nervous system excitation including hallucination and cocaine-like cardiovascular stimulation increasing myocardial oxygen demand. It is usually used with a benzodiazepine either by intermittent use or by infusion. We use a 10:1 mixture of ketamine and midazolam by infusion. Its bronchodilator effects can be used in severe asthma.

**Etomidate**
Etomidate is rarely used for continuous sedation of critically ill patients. It is associated with an increased mortality since it inhibits cortisol production and can induce an ‘Addisonian’ crisis.

**Thiopentone**
The use of thiopentone is restricted to a few specific indications. Status epilepticus is one, cerebral protection another one. Thiopentone induced cerebral vasoconstriction reduces cerebral blood flow and subsequently intracranial pressure. Cerebral metabolic demand is halved. Although theoretically possible that it has a beneficial effect in patients with head injuries this remains unproven. The half-life of thiopentone is 11 h and, if used as continuous infusion, the metabolite pentobarbitone accumulates. The prolonged cumulative effect makes its use for sedation in the critically ill patient unsuitable because patients are slow to awaken.

**Inhalation agents**

**Nitrous oxide**
The use of nitrous oxide for sedation is rare. If used for longer than 6 h it causes interference with vitamin B₁₂ and folic acid metabolism. Myelodepression, myopathy and a neuropathy result. In critically ill patients, adverse effects may appear early after 2 h. Nitrous oxide also causes environmental pollution.

**Isoflurane**
Ether, halothane and enflurane have been used, mostly in patients with status asthmaticus. Today, isoflurane is the only volatile anaesthetic agent used in the critically ill. Isoflurane is delivered into the ventilator circuit at a concentration of 0.1–0.6%. This provides satisfactory sedation and recovery is rapid. In low concentration it has haemodynamic stability and a lack of hepatic, renal and adrenal toxicity. Agitation, hallucination and ataxia have been reported but these effects...
resolve spontaneously and completely. Of all the volatile agents, isoflurane is minimally metabolised. However, 0.2% of isoflurane is still metabolised resulting in the release of fluoride. It is noteworthy that when serum fluoride concentration has been measured, it never approached toxic levels and renal function is unaffected. Tolerance has not been a problem. The main hindrance for its widespread use for sedation is its expense (£100 per day), similar to propofol, and for the need for additional equipment such as vaporisers and scavanging facilities.

**Sedation for the acute confusional state**

The management of the acutely confused patient who is breathing spontaneously can be difficult. Oral benzodiazepines, such as temazepam or diazepam, may help to facilitate ‘a good night’s sleep’, but attempts to control an agitated patient with benzodiazepines may result in overdosage and paradoxical confusion.

Major tranquilizers, such as butyrophenones and phenothiazines, can be useful to treat agitated and confused patients. Their effect is sedative and antipsychotic. Haloperidol and chlorpromazine are the most commonly used drugs. Anticholinergic and α-adrenergic blocking activity are the main limiting side effects.

**Other agents**

Clonidine has been successfully used in the treatment of fear, anxiety and sleep disturbances associated with the withdrawal of opioids. As an α₂-agonist it reduces noradrenaline release within the locus cerulius where prolonged opioid use causes up regulation of postsynaptic adrenergic receptors. Doses of 100–200 mg every 4–6 h have been used, but the tendency to cause hypotension limits its use.

Chloral hydrate often used in paediatric practice is a useful sedative inducing sleep. In renal failure, the accumulation of active metabolites can pose a risk.

Chlormethiazole can be indicated in delirium tremens, status epilepticus, eclampsia and acute confusional states. After short infusions, recovery is rapid owing to redistribution but infusions longer than 48 h delay recovery. Other side effects are nasal irritation, thrombophlebitis, haemolysis and fluid overload.

**Tolerance**

Tolerance is almost universal with almost all CNS depressants. First recognised with alcohol and opioids used socially, it is now well
described with the drugs used for sedation and analgesia. Tolerance is easy to deal with at first necessitating merely an increase in dose. However, when the dose becomes excessive then it may hazard the patient. The increase in dose may result in large amounts of drugs being given to the patient that they may not be able to eliminate. This can cause prolonged coma. Alternatively, large amounts of a potentially toxic solvent may be given. Each ICU should establish the maximum amount of drug to use routinely in their patients. Occasionally these will be exceeded, but only with a great deal of thought. When the maximum levels are reached, we would normally change to another drug with a similar action, but a different mechanism of action.

A practical approach to sedation

On admission to the ICU, the critically ill patient often requires resuscitation, ventilation and establishment of invasive monitoring lines. For this time sedation, analgesia and muscle relaxation for a short interval are useful. Afterwards lighter levels of sedation are needed. We use incremental boluses of morphine, 2.5 mg and midazolam 2.5 mg as required in adults. The disadvantages of intermittent boluses is the high nursing input necessary and the risk of intermittent over and under dosage with associated haemodynamic instability. If frequent intermittent doses are needed, a continuous intravenous infusion can be started. The morphine and midazolam maintenance doses are approximately 1–5 mg/h. Unnecessary use of infusions may induce tolerance and result in accumulation.

Consciousness levels need to be assessed on an hourly basis using a sedation scale. Daily reviews of the need of continuous infusions are important. As soon as weaning from the ventilator is planned, midazolam and morphine doses can be reduced or changed over to the shorter acting propofol at 1–3 mg/kg/h – or alfentanil at 0.5–0.1 μg/kg/h. Alfentanil is useful for short-term analgesic supplementation and to prevent autonomic response to painful stimuli1,4,12,24. In the future, remifentanil may prove a more suitable alternative21.

No one drug will make every patient comfortable in the ICU. The patient’s attendants need to have the right skills and knowledge to be able to safely use combinations of drugs in the critically ill.

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