Analgesia and sedation in critically ill children

Stephen D. Playfor MD

Key points
Adequate analgesia should be provided to all critically ill children, regardless of the need for sedation.
Morphine and midazolam remain the most commonly used analgesic and sedative agents, respectively, in the UK.
Regular assessment of pain and sedation levels using appropriate tools is recommended in the paediatric intensive care unit.
There are no proven evidence-based techniques to prevent the incidence of withdrawal syndrome.

Effective analgesia and sedation for critically ill children involve caring for both their physical and psychological comfort. All critically ill children in a paediatric intensive care unit (PICU) have the right to adequate pain relief. Any correctable environmental and physical factors causing discomfort should be addressed before the introduction of pharmacological agents: a normal pattern of sleep should be encouraged, and attention should be paid to the provision of feeding and hydration, lighting, environmental noise, and the temporal orientation of patients.

Once an adequate level of analgesia has been achieved, additional sedative agents may be required by some children. The aims of sedation are to reduce anxiety and distress in the child, and to allow for better tolerance of therapeutic and diagnostic procedures. Facilitation of mechanical ventilation is particularly important with the application of less physiological ventilatory modes such as high-frequency oscillatory ventilation, controlled hypoventilation, and tracheal gas insufflation. Further benefits of sedation may include reduced metabolic rate and oxygen demand, enhanced analgesia, a less disrupted sleep pattern, and reduced patient recall of unpleasant interventions. It is well recognized that insufficient sedation is a risk factor for inadvertent self-extubation.

Current practice
There is considerable variation in the provision of analgesia and sedation for critically ill children. In a recent prospective observational study of 338 critically ill children in 20 UK PICUs, a total of 24 different sedative and analgesic agents were administered.1 Multiple surveys have shown that the most commonly used sedative and analgesic agents for critically ill children in the UK are midazolam and morphine,2 whereas in the USA, surveys show that midazolam and fentanyl predominate.3 In critically ill adults, continuous infusions of sedative agents have been associated with prolonged periods of mechanical ventilation and a routine daily discontinuation of intravenous sedative agents is now recommended.4 This practice has been associated with a reduction in duration of mechanical ventilation and duration of intensive care admission, without any apparent adverse psychological effects. This approach has not yet been evaluated in critically ill children where the potential adverse effects of discontinuing sedative agents include inadvertent self-extubation, adverse cardiovascular effects, and possible negative psychological outcomes. However, it has already been demonstrated that increased sedative use in the first 24 h of weaning from mechanical ventilation is associated with failure of extubation in infants and children.

Analgesic agents
The dosing schedules of analgesic agents commonly used in PICU are shown in Table 1. Commonly used analgesic agents include opioids for the relief of severe pain, non-steroidal anti-inflammatory drugs (NSAIDs) for moderately severe pain, and paracetamol for the treatment of mild to moderate pain. Regional techniques are also utilized.

Regional analgesia
Subcutaneous or topically administered local anaesthetics are used in critically ill children for the short-term relief of painful procedures. Regional techniques such as epidural anaesthesia and peripheral nerve blocks are also being used more frequently. The pharmacokinetics and pharmacodynamics of systemic analgesic agents alter with age. Neonates frequently demonstrate reduced clearance of agents because of hepatic enzyme system immaturity, whereas children aged 2–6 yr may demonstrate greater weight-indexed clearance than adults because of their relatively large liver mass.

Opioids
Opioids produce analgesia via a variety of central and peripheral opioid receptors, particularly the μ- and κ-receptors. It is understood

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that interaction at other receptors may be responsible for adverse effects associated with these agents.

**Morphine**

Morphine is the only poorly lipid soluble opioid in common use. When administered in a single dose of 0.1 mg kg\(^{-1}\) i.v., its peak analgesic effect occurs after 20 min and its duration of action is \(\sim 4\) h. Morphine undergoes extensive hepatic and extra-hepatic glucuronidation and metabolites are excreted primarily in the urine. The removal of morphine from the body is slow and quantitatively different in newborns, but adjusts towards adult values within the first 6 months of life. Morphine may stimulate the release of significant amounts of histamine and inhibits compensatory sympathetic responses; the vasodilation produced by morphine may result in hypotension particularly after bolus administration. Discontinuation of morphine infusions has been associated with withdrawal phenomena, which may include pupillary dilatation, lachrymation, sweating, goose pimples on the skin, hypertension, pyrexia, vomiting, abdominal pain, diarrhoea, muscle and joint pains, and behavioural changes.

**Fentanyl**

Fentanyl is a synthetic opioid with \(\sim 100\) times the analgesic potency of morphine. It is highly lipid soluble, which accounts for its rapid onset of action. Fentanyl administration causes less histamine release than morphine, and therefore less hypotension. However, fentanyl can reduce cardiac output by decreasing the heart rate, which may be an advantage in situations where ablation of the stress response is desirable. When given intravenously, fentanyl has a relatively short half-time of 30–60 min owing to rapid redistribution to peripheral compartments. With prolonged administration, there is accumulation within these peripheral compartments causing an increase in the context sensitive half-time and tolerance may rapidly develop. Metabolism occurs almost exclusively in the liver and clearance is markedly affected by hepatic blood flow. Fentanyl has no active metabolites, and there is no cross-reactivity in patients with morphine allergy.

**Remifentanil**

Remifentanil is a relatively new synthetic opioid: a phenylpiperidine derivative, which acts as a pure \(\mu\)-receptor agonist, is equipotent to fentanyl, but has unique properties. Its cardiorespiratory effects are similar to those of other opioids. Remifentanil has an exceptionally short half-time of 3 min in all age groups as it is metabolized by plasma and tissue esterases and has a very small volume of distribution. The effects of remifentanil dissipate rapidly, even after prolonged infusion, giving it a very short context sensitive half-time. Remifentanil has been used to provide ongoing analgesia in PICU although prolonged use of this agent is associated with the rapid development of tolerance and relatively high cost. This agent may have more potential for procedural analgesia in the critical care setting given its rapid onset and offset

### Table 1 Recommended analgesic and sedative agents in patient-controlled analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing information</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Intravenous bolus; (&lt;60) kg: 100–200 (\mu)g kg(^{-1})</td>
<td>Potential histamine release; consider reduced dose in renal and hepatic impairment</td>
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<tr>
<td></td>
<td>&gt; 60 kg: 5–10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous infusion; (&lt;60) kg: 10–60 (\mu)g kg(^{-1}) h(^{-1})</td>
<td></td>
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<tr>
<td></td>
<td>&gt; 60 kg: 0.8–3 mg h(^{-1})</td>
<td></td>
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<tr>
<td>Fentanyl</td>
<td>Intravenous bolus; (&lt;60) kg: 1–2 (\mu)g kg(^{-1})</td>
<td>Rapid onset; relatively long elimination half-time, especially after prolonged use</td>
</tr>
<tr>
<td></td>
<td>&gt; 60 kg: 50–200 (\mu)g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous infusion; (&lt;60) kg: 4–10 (\mu)g kg(^{-1}) h(^{-1})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 60 kg: 25–100 (\mu)g h(^{-1})</td>
<td></td>
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<tr>
<td>Paracetamol</td>
<td>(&lt;60) kg: 10–15 mg kg(^{-1}) 4 h(^{-1})</td>
<td>Rectal administration associated with variable uptake</td>
</tr>
<tr>
<td></td>
<td>&gt; 60 kg: 650–1000 mg 4 h(^{-1})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max daily dose; (&lt;3) months; 60 mg kg(^{-1}) day(^{-1})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months–12 yr; 90 mg kg(^{-1}) day(^{-1}) &gt;12 years; 4 g day(^{-1})</td>
<td></td>
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<tr>
<td>Ibuprofen</td>
<td>(&lt;60) kg: 6–10 mg kg(^{-1}) 6 h(^{-1})</td>
<td>Use with caution in renal disease; water retention; potential for gastrointestinal and bleeding</td>
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<td></td>
<td>&gt; 60 kg: 200–600 mg h(^{-1})</td>
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<td></td>
<td>Max daily dose; (&lt;60) kg; 30 mg kg(^{-1}) day(^{-1})</td>
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<td></td>
<td>&gt; 60 kg: 2.4 g day(^{-1})</td>
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<tr>
<td>Midazolam</td>
<td>Intravenous bolus; (&lt;60) kg: 0.1–0.2 mg kg(^{-1})</td>
<td>Problems with tolerance and withdrawal syndrome; possible prolonged sedation on discontinuation</td>
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<tr>
<td></td>
<td>&gt; 60 kg: 5 mg</td>
<td></td>
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<tr>
<td></td>
<td>Intravenous infusion; (&lt;60) kg: 2–10 (\mu)g kg(^{-1}) min(^{-1})</td>
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<tr>
<td></td>
<td>&gt; 60 kg: 5–15 mg h(^{-1})</td>
<td></td>
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<tr>
<td>Clonidine</td>
<td>Intravenous infusion; 0.1–2 (\mu)g kg(^{-1}) h(^{-1})</td>
<td>May be associated with withdrawal syndrome; avoid sudden discontinuation</td>
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<tr>
<td></td>
<td>NG: 1–5 (\mu)g kg(^{-1}) 8 h(^{-1})</td>
<td></td>
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<tr>
<td>Chloral hydrate/Triclofos</td>
<td>NG: 20–50 mg kg(^{-1}) 4–6 h(^{-1})</td>
<td>Triclofos may cause less gastric irritation; risk of accumulation</td>
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<td>Maximum 2 g per dose</td>
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<tr>
<td>Promethazine</td>
<td>NG: 1–2 mg kg(^{-1}) 6 h(^{-1})</td>
<td>Use with caution in neonates</td>
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<tr>
<td></td>
<td>Maximum 50 mg per dose</td>
<td></td>
</tr>
<tr>
<td>Alimemazine (Trimeprazine)</td>
<td>NG: 2–4 mg kg(^{-1}) 6 h(^{-1})</td>
<td>Avoid in renal and hepatic failure</td>
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times and effective blunting of airway reflexes, although respiratory and cardiovascular depressant effects should be anticipated in this setting.

**NSAIDs and paracetamol**

NSAIDs provide analgesia through the non-selective, competitive inhibition of cyclo-oxygenase, a critical enzyme in the inflammatory cascade. Although the administration of NSAIDs has been shown to significantly reduce opioid requirements in adult and paediatric pain after surgery by ~15–30%, the analgesic benefits of NSAIDs have not been systematically studied in critically ill children. Paracetamol is an analgesic used to treat mild to moderate pain. When used in combination with opioid agents, paracetamol produces a greater analgesic effect than higher doses of opioid alone, and it has been shown to have an opioid-sparing effect in adults.

**Sedative agents**

The dosing schedules of sedative agents commonly used in PICU are shown in Table 1.

**Benzodiazepines**

Benzodiazepines have specific activity at gamma-aminobutyric acid receptors, which form part of the major inhibitory system of the central nervous system. The most commonly used benzodiazepines for sedation in PICU are midazolam, lorazepam, and diazepam.

**Midazolam**

Midazolam is a sedative agent which also produces antegrade amnesia without impairing the ability to retrieve previously learned information. It is presented as a water-soluble acidic preparation, which at plasma pH converts into an un-ionized form that crosses the blood brain barrier rapidly; it has the shortest elimination half-time of the benzodiazepine group. After a single bolus i.v. injection, the time to peak sedation is 5–10 min with a duration of action of 30–120 min. When given by continuous intravenous infusion, the duration of action is significantly longer and, after prolonged administration, sedation effects may persist for 48 h after discontinuation of the agent.

Midazolam is metabolized to 1-hydroxymidazolam and 1,4-dihydroxymidazolam by cytochrome P450 isoenzyme 3A4 hydroxylation, and then undergoes glucuronidation. Accumulation of active metabolites may produce prolonged sedative effects in patients with renal insufficiency, while substrate competition for cytochrome P450 isoenzyme 3A4 may also occur leading to prolonged sedation after the co-administration of certain pharmacological agents including erythromycin. The main adverse events are the development of tolerance, dependence, and withdrawal after subsequent discontinuation. Hypotension may occur, particularly after bolus administration in the setting of hypovolaemia. There is also evidence of reduced sedative efficacy when midazolam is administered to younger children.

**Clonidine**

Clonidine is a sedative agent being used with increasing frequency to provide sedation in critically ill children in the UK. It is an α2-adrenoreceptor agonist which produces sedation without causing respiratory depression, and exerts an anxiolytic effect that is comparable with that of benzodiazepines. These agents reduce the requirement for other sedatives and can improve haemodynamic and sympathoadrenal stability. The α2-adrenoreceptor agonists also have analgesic properties, which are probably mediated through the prevention of substance P release. Adverse effects associated with the use of clonidine include bradycardia and hypotension; withdrawal after prolonged administration has been associated with hypertension and seizures. Therefore, abrupt discontinuation of clonidine should be avoided.

**Enteral sedative agents**

It is a common practice in the UK to introduce enteral sedative agents when this route of administration is available. The most commonly used drugs include the hypnotics (e.g. chloral hydrate or triclofos sodium) and the sedating antihistamines [e.g. promethazine or alimemazine (trimeprazine)]. Chloral hydrate and promethazine, when used in combination, have been shown to be more effective than i.v. midazolam in providing maintenance sedation in critically ill children. Chloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 15–60 min. It is converted to the active metabolite trichloroethanol and is metabolized in the liver and other tissues and excreted in the urine and bile. The typical duration of action of 60–120 min may be prolonged in renal or hepatic disease. There is a risk of drug accumulation with repeated high doses. Gastrointestinal irritation is the most commonly reported adverse effect although Triclofos sodium is believed to cause fewer gastrointestinal disturbances than chloral hydrate.

**Assessment of analgesia and sedation**

**Pain assessment**

Pain is a subjective experience and, provided there is no clear reason to doubt them, a patient’s self-report is the single most reliable indicator of pain and must be considered the standard against which to guide analgesic therapy. Although it is clear that pain-related behaviours and the physiological indicators of pain are neither sensitive nor specific to pain, these features should be routinely documented, especially in those who are unable to communicate normally.

In neonates, infants, and children aged <3 yr, behavioural observational scales are the primary tools available for the assessment of pain. These scales frequently rely on facial expression, motor responses, and physiological indices. The assessment of
pain in young children is extremely challenging; one should consider pathophysiological states and therapeutic interventions that are known to be painful, and also involve the patient’s family in the assessment.

Children aged 3–8 yr are generally able to use self-reporting techniques such as ‘faces scales’ using either photographs or drawings of faces, although their application in the critical care environment is often difficult and largely unvalidated. Competent children aged >8 yr can usually use more validated unidimensional tools, such as verbal rating scale, visual analogue scale, and numeric rating scale in the same way as adults.

Sedation assessment

In order to avoid the potential complications of both excessive and inadequate sedation, the level of sedation of critically ill children should be regularly assessed and documented. The use of a formal sedation assessment scale is recommended, wherever possible using a validated scoring system such as the COMFORT scale. This is a subjective physiological and behavioural scoring system, which requires no disturbance to the patient. It measures eight variables: mean arterial blood pressure, heart rate, muscle tone, facial tension, alertness, calmness/agitation, respiratory behaviour, and physical movement after a 2 min period of observation. It must be remembered that the desired level of sedation will vary for an individual patient according to the underlying pathophysiological process and the nature of required therapeutic, invasive, or investigative procedures. Administered doses of sedative agents should be titrated according to these fluctuating requirements and in light of frequently repeated assessments to ensure the desired level of sedation is always being provided.

Neurophysiological monitors

Clearly, the COMFORT scale, and other similar systems based on patient responsiveness, cannot be used during the administration of neuromuscular blocking agents and can be difficult to interpret during deep sedation. This adds to the potential benefits of an objective measurement of sedation using neurophysiological techniques such as the bispectral index (BIS) or auditory-evoked potentials.

Considerable interest exists in the use of electroencephalogram (EEG) analysis tools such as BIS which uses a digital scale from 100 (completely awake) to 0 (isoelectric EEG). The analysis of the BIS score has been found to reliably differentiate between inadequate and adequate levels of sedation, but appears to be relatively insensitive in distinguishing between adequate and excessive sedation. Comparisons of BIS and COMFORT scale measurements at isolated moments during a prolonged critical care admission are not well correlated, and BIS scores may vary between patients at the same subjective level of sedation, particularly at the deeper levels of sedation as defined by the COMFORT scale. BIS also has technical limitations in PICU as a result of polypharmacy and electrical interference. Presently, there is insufficient evidence to support the routine use of the BIS monitor in the PICU.

Clinical practice guidelines

The introduction of clinical guidelines has been associated with a significant reduction in sedative costs per bed day in adult critical care units. Consensus clinical practice guidelines for the provision of sedation and analgesia in critically ill children were published in 2006 by the UK Paediatric Intensive Care Society. A summary of the recommendations is shown in Box 1.

Withdrawal syndrome

A withdrawal syndrome may occur after the discontinuation of sedative and analgesic agents, particularly benzodiazepines and opioids. Withdrawal syndrome is related to the total drug dose, duration of administration, or both. Thus, withdrawal syndrome after midazolam (incidence ~17–30%) is associated with a total dose of >60 mg kg$^{-1}$. Similarly, a total fentanyl dose of >1.5 mg kg$^{-1}$ is associated with a >50% chance of the developing withdrawal syndrome, while infusion of fentanyl for more than 9 days in infants is 100% predictive of the syndrome.

Features of withdrawal syndrome usually occur within a few hours of stopping the drug responsible. These may include: (i) central nervous system manifestations (e.g. agitation, seizures, hallucinations, and psychosis), (ii) autonomic features (e.g. vomiting, tachycardia, hypertension, and fever), and (iii) cardiovascular effects (e.g. arterial desaturation). Assessment of withdrawal syndrome is hampered by the lack of a validated PICU assessment system; many institutions utilize modified scoring systems developed from those used to assess neonatal abstinence syndrome.

Although tolerance, physical dependence, and eventual withdrawal syndrome can be anticipated when patients have been given high doses or prolonged infusions of opioids and sedative agents, the exact cellular mechanisms responsible for the development of withdrawal remain poorly defined. There is little evidence upon which to base recommendations regarding its prevention, assessment, and management in critically ill children. Commonly used strategies to reduce the incidence of withdrawal syndrome begin with efforts to reduce the total doses of benzodiazepines and opioids administered in PICU by using sedation and pain scoring systems and through the application of the non-pharmacological interventions. Adult sedative and analgesic guidelines recommend the routine tapering of sedative agents and opioids in high-risk patients to minimize the risk of withdrawal, and it is standard practice in many paediatric units to taper doses by daily increments of 5–10% of the final dose. Other approaches include the planned substitution of one class of agent for another (‘drug holidays’) and the use of long-acting preparations of parenteral agents (e.g. lorazepam and clonidine), enteral agents (e.g. diazepam, clonidine, methadone, and oral morphine preparations), and novel delivery routes (e.g. subcutaneous and transdermal administration of fentanyl).
Box 1 Summary of recommendations for sedation and analgesia in critically ill children

1. All critically ill children have the right to adequate relief of their pain.
2. Any correctable environmental and physical factors causing discomfort should be addressed alongside the introduction of pharmacological agents.
3. A normal pattern of sleep should be encouraged. Attention should be paid to lighting, environmental noise, and temporal orientation of patients.
4. Pain assessment should be performed regularly by using a scale appropriate to the age of the patient and routinely documented. The level of pain reported by the patient must be considered the current standard of analgesia.
5. Patients who cannot communicate should be assessed for the presence of pain-related behaviours and physiological indicators of pain.
6. A therapeutic plan for analgesia should be established for each patient and regularly reviewed.
7. Continuous intravenous infusions of morphine or fentanyl are recommended for relief of severe pain.
8. Non-steroidal anti-inflammatory drugs or paracetamol may be used as adjuncts to opioids in certain patients.
9. Local and regional anaesthetic techniques should be considered.
10. A patient-controlled analgesia device may be useful in older children.
11. Adequate analgesia should be provided to all critically ill children regardless of the need for sedation.
12. The level of sedation should be regularly assessed and documented using a sedation assessment scale, wherever possible using a validated scoring system such as the COMFORT scale.
13. The desired level of sedation should be identified for each patient and should be regularly reassessed.
14. Doses of sedative agents should be titrated to produce the desired level of sedation.
15. Midazolam is the recommended agent for the majority of critically ill children requiring intravenous sedation. It should be given by continuous infusion.
16. Clonidine given by continuous intravenous infusion may be used as an alternative sedative agent to midazolam.
17. Propofol should not be used to provide continuous sedation in critically ill children.
18. Early use of enteral sedative agents is recommended.
19. The use of clinical guidelines for sedation is recommended.
20. The potential for opioid and benzodiazepine withdrawal syndrome should be considered after seven days of continuous therapy. When subsequently discontinued, the doses of these agents may need to be routinely tapered.

References


Please see multiple choice questions 10–13.