Analgesia and sedation in critically ill children
S D Playfor
doi:10.1136/adc.2007.119628

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Providing effective analgesia and sedation for critically ill children means addressing both their physical and psychological comfort. Correctable environmental and physical factors causing discomfort should be dealt with in the first instance; these factors might include medical devices, beds, lighting, noise reduction strategies, fluid and feeding regimes, day-night orientation and maintenance of sleep structure. Factors such as these should be considered before the introduction of any pharmacological agents, and should be continually reassessed during the course of a critical care admission.

After a satisfactory level of analgesia has been achieved, additional sedative agents may be required by some children. The aims of sedation are to reduce levels of anxiety and distress in the child, and to allow for better tolerance of therapeutic or diagnostic procedures. The specific strategies employed to achieve satisfactory levels of analgesia and sedation in critically ill children will depend on whether prolonged sedation is required, as is normally needed to facilitate invasive mechanical ventilation, or if short-term sedation is required to facilitate a procedure. The requirement profile for sedative agents in critically ill children can vary considerably during the course of their admission; a young child mechanically ventilated for a week may require a gradually increasing level of “background” sedation to allow them to tolerate tracheal intubation, particularly if tolerance to sedative agents develops, and in addition they may require several episodes of controlled deepening of sedation to facilitate specific procedures.

In both cases, environmental and non-pharmacological techniques can reduce the need for pharmacological agents. Massage and relaxation techniques have been shown to be beneficial in critically ill adults and the watching of videos has also been shown to reduce the sedation requirements of children undergoing procedures. The benefits of music therapy in critically ill adults have been well described and can decrease anxiety and promote relaxation. Play specialists have an important role in the paediatric intensive care unit (PICU), assessing children and providing individualised distraction therapy using music, relaxation techniques, fibre optic lights and bubble tubes. Communication, continual reorientation in time and place, and the presence of relatives can all reduce anxiety.

**PROLONGED ANALGESIA AND SEDATION**

One of the primary goals of sedation is to improve tolerance of tracheal intubation and mechanical ventilation; particularly with less physiological modes such as high frequency oscillation, or controlled hypoventilation. Further benefits of prolonged sedation may include a reduction in metabolic rate and oxygen demand, enhanced analgesia, better preservation of sleep structure and reduced patient recall of unpleasant interventions. Insufficient sedation has also been demonstrated as a risk factor for inadvertent self-extubation.

In adults, continuous infusions of sedative agents have been associated with prolonged periods of mechanical ventilation and prolonged intensive care admission. It has been suggested that a routine daily discontinuation of intravenous sedative agents may be of benefit in adult patients, although this approach has not been evaluated in critically ill children where the potential adverse effects include inadvertent self-extubation and possible negative psychological outcomes.

Clinical practice guidelines for prolonged analgesia and sedation have been available for adult patients from the Society of Critical Care Medicine and the American College of Critical Care Medicine since 1995. More recently the United Kingdom Paediatric Intensive Care Society’s Sedation, Analgesia and Neuromuscular Blockade Working Group has produced consensus guidelines in this area. The key findings of the Working Group are shown in box 1. The development of these clinical guidelines was hampered by the lack of high quality evidence in the literature relevant to children; very few randomised controlled trials of sedative agents have been performed in critically ill children.

Accurate assessment of analgesia and sedation is not possible in patients who are receiving continuous infusions of neuromuscular blocking agents. Whenever it is safe to do so, continuous infusions of neuromuscular blocking agents should be discontinued at least once in every 24-hour period until spontaneous movement returns so that levels of analgesia and sedation can be assessed.

**ANALGESIA**

Pain is a subjective experience, and in the absence of a clear reason to doubt them, the patient’s report is the single most reliable indicator of pain and should be considered the standard against which to guide analgesic therapy. It is important to remember that unrelieved pain has adverse physical and psychological consequences.

In addition to systemic pharmacological agents, local anaesthetics, regional techniques (such as...
Pharmacy update

Box 1 Recommendations for analgesia and sedation 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 (PCA) 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 be routinely tapered.

COMMONLY USED AGENTS

Recommended analgesic agents, doses and prescribing notes are shown in table 1. Opioids produce analgesia via a variety of central and peripheral opioid receptors, particularly µ- and κ-receptors, and it is believed that interaction with other receptors may be responsible for the adverse effects associated with these agents. To varying degrees the opioids tend to produce hypotension and respiratory depression. Research has shown that the most commonly used analgesic agents for severe pain in the PICU are morphine in the UK and fentanyl in the USA.

1. Morphine

Morphine has a relatively long duration of action of around two hours when administered as a single dose and has a peak analgesic effect 20 minutes after intravenous administration. Morphine may result in the release of significant amounts of histamine and inhibits compensatory sympathetic responses; the resultant vasodilatation may result in hypotension, particularly following bolus administration. The metabolism of morphine produces an active metabolite, morphine-6-glucuronide, the elimination of which may be delayed in renal disease, and the inactive metabolite morphine-3-glucuronide which does not bind to opioid receptors. Discontinuation of morphine infusions has been associated with withdrawal phenomena which may include behavioural changes, pupillary dilatation, lacrimation, sweating, goose pimples, hypertension, pyrexia, vomiting, abdominal pain, diarrhoea, muscle and joint pains.

2. Fentanyl

Fentanyl is a potent synthetic opioid with a rapid onset of action, which is associated with less histamine release than morphine, and therefore produces less hypotension; although it may reduce cardiac output by decreasing the heart rate. When given intravenously there is rapid redistribution to peripheral compartments, giving fentanyl a relatively short half-life of 30–60 minutes. After prolonged administration however there is accumulation causing an increase in the context-sensitive half-time and tolerance may rapidly develop.

3. Remifentanil

Remifentanil is a synthetic opioid with cardiorespiratory effects similar to other opioids and which is equipotent to fentanyl. Remifentanil has an exceptionally short half-life of 3 minutes in all age groups because it is metabolised by plasma and tissue esterases and therefore has a very small volume of distribution—regardless of the duration of infusion—resulting in a very short context-sensitive half time. Remifentanil has been used to provide ongoing analgesia in the PICU although prolonged use of this agent is associated with the rapid development of tolerance.

PAIN ASSESSMENT

Although difficult to use in practice, behavioural observational scales are the primary tools available for pain assessment in infants and children under three years of age. These scales use facial expression, motor responses and physiological parameters to assess pain.

For children aged 3–8 years, self-reporting techniques such as ‘faces scales’ using either photographs or drawings of faces may be used to assess pain. Above the age of 8 years, competent children can usually use uni-dimensional tools, such as the visual analogue scale (VAS) or the numeric rating scale (NRS).
Table 1 Recommended analgesic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing information</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Intra-venous bolus</td>
<td>Potential histamine release Consider reducing dose in renal and hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 100–200 μg/kg/dose</td>
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<tr>
<td></td>
<td>&gt;60 kg: 5–10 mg/dose</td>
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<tr>
<td></td>
<td>Intra-venous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 10–60 μg/kg/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 0.8–3 mg/h</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Intra-venous bolus</td>
<td>Rapid onset &amp; relatively long elimination half-life, especially following prolonged use</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 1–2 μg/kg/dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 50–200 μg/dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-venous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 4–10 μg/kg/h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 25–100 μg/h</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>&lt;60 kg: 10–15 mg/kg/dose, 4 hourly</td>
<td>Rectal administration is associated with variable uptake</td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 650–1000 mg/dose, 4 hourly</td>
<td>Intravenous preparation available</td>
</tr>
<tr>
<td></td>
<td>Max daily dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3 months; 60 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months–12 years; 90 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;12 years; 4 g/day</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>&lt;60 kg: 6–10 mg/kg/dose, 6 hourly</td>
<td>Use with caution in renal failure Potential for gastrointestinal bleeding and water retention</td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 200–600 mg/dose, 6 hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max daily dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 30 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 2.4 g/day</td>
<td></td>
</tr>
</tbody>
</table>

NSAIDs and paracetamol
Non-steroidal anti-inflammatory agents (NSAIDs) provide analgesia through the non-selective, competitive inhibition of cyclooxygenase (COX), which is a critical enzyme in the inflammatory cascade. The administration of NSAIDs has been shown to significantly reduce opioid requirements in adult and paediatric pain following surgery by around 15–50%.[21] Paracetamol is an analgesic used to treat mild to moderate pain which, when used in combination with opioid agents, produces a greater analgesic effect than higher doses of opioid alone.

SEDATION
Research has shown the most commonly used intravenous agent to provide prolonged sedation in children is midazolam, although there is considerable variation in clinical practice. Table 2 shows doses of the commonly used sedative agents.

SEDATION ASSESSMENT
PICU staff informally assess the depth of sedation of their patients on a continual basis, but wherever possible the level of sedation should be assessed and documented using a validated sedation assessment scale such as the COMFORT scale.[22] Neurophysiological techniques such as the bispectral index (BIS) or auditory evoked potentials have also been used in the critical care environment but there is currently insufficient evidence to support the routine use of the BIS monitor, or any other neurophysiological sedation scoring technique, in the PICU.[23]

SEDATIVE DRUGS
Benzodiazepines
Benzodiazepines have specific activity at gamma amino butyric acid (GABA) receptors, which form part of the primary inhibitory system of the central nervous system. The benzodiazepines most commonly used for sedation in the PICU are midazolam, lorazepam and diazepam. Midazolam is an excellent agent for inducing antegrade amnesia without impairing the ability to retrieve previously learned information, even at low levels of sedation.[24] Midazolam has the shortest elimination half-life of the benzodiazepine group; the time to peak sedation is 5–10 minutes following intravenous injection with a duration of action of 30–120 minutes. When given by continuous intravenous infusion the duration of action is significantly longer and if given for more than a week, sedation may last for 48 hours following discontinuation of the agent.

Midazolam is metabolised by hydroxylation to 1-hydroxymidazolam and 1,4-dihydroxymidazolam by cytochrome P450 isozyme 3A4, and is then glucuronidated.[25] In patients with renal insufficiency prolonged sedative effects may be caused by the accumulation of active metabolites, similarly, substrate competition may also occur leading to prolonged sedation following the co-administration of certain other drugs such as erythromycin.[26] The main adverse events associated with midazolam are tolerance, dependence and withdrawal following discontinuation. Hypotension may occur but is most likely with bolus administration, particularly in the setting of hypovolaemia, and there is evidence of reduced sedative efficacy in infants.[27]

Clonidine
Clonidine is an α₂-adrenoreceptor agonist which produces sedation without causing respiratory depression, and exerts an anxiolytic and analgesic effect. Clonidine may reduce the requirement for other sedative agents and improve haemodynamic stability. Adverse effects associated with the use of clonidine include bradycardia and hypotension.

Enteral sedative agents
Where the enteral route is available, enteral sedatives such as the hypnotic agents chloral hydrate or triclofos sodium, and sedating antihistamines such as promethazine or alimemazine (trimeprazine) are recommended.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and starts to act within 15–60 minutes. Gastrointestinal irritation is the most commonly reported adverse effect and Triclofos sodium is believed to result in fewer gastrointestinal disturbances.

Volatile agents
Volatile anaesthetic agents have been used to provide sedation in the critical care setting for around 50 years. The technique has not become
**Recommended sedative agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing information</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Intravenous bolus</td>
<td>May be associated with tolerance and withdrawal syndrome</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 0.1–0.2 mg/kg/dose</td>
<td>Prolonged sedation possible on discontinuation</td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 5 mg/dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 2–10 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 kg: 5–15 mg/h</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Intravenous infusion</td>
<td>May be associated with withdrawal syndrome</td>
</tr>
<tr>
<td></td>
<td>0.1–2 μg/kg/hr</td>
<td>Avoid sudden discontinuation</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>NG: 1–5 μg/kg/dose 8 hourly</td>
<td>May cause gastric irritation</td>
</tr>
<tr>
<td>Triclofos</td>
<td>NG: 20–50 mg/kg/dose 4–6 hourly</td>
<td>Risk of accumulation</td>
</tr>
<tr>
<td></td>
<td>Maximum 2 g per dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max daily dose: 200 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>NG: 1–2 mg/kg/dose 6 hourly</td>
<td>Use with caution in neonates</td>
</tr>
<tr>
<td></td>
<td>Maximum 50 mg per dose</td>
<td></td>
</tr>
<tr>
<td>Alimemazine (Trimeprazine)</td>
<td>NG: 2–4 mg/kg/dose 6 hourly</td>
<td>Use with caution in renal and hepatic failure</td>
</tr>
<tr>
<td></td>
<td>Maximum 90 mg per dose</td>
<td></td>
</tr>
</tbody>
</table>

**WITHDRAWAL SYNDROME**

Withdrawal syndrome may occur following the discontinuation of analgesic and sedative agents, particularly benzodiazepines and opioids, and is believed to be related to the total dose of drug received. The incidence of midazolam withdrawal syndrome is quoted as being between 17% and 50%. Features of withdrawal syndrome usually occur within a few hours of stopping the drug in question and can include central nervous system manifestations (agitation, seizures, arterial desaturation, hallucinations and psychosis) and autonomic features (vomiting, tachycardia, hypertension and fever). Assessment of withdrawal syndrome is hampered by the lack of a validated PICU assessment tool; many institutions use modified scoring systems developed from those used to assess neonatal abstinence syndrome such as those developed by Finnegan. One of the key difficulties is that many of the features of opioid withdrawal overlap with those of benzodiazepine withdrawal, as was recently highlighted by Ista and colleagues.

There is little evidence upon which to make recommendations regarding the prevention, assessment and management of withdrawal syndrome in critically ill children. There is scant evidence to support the routine tapering of sedative agents and opioids or the planned substitution of one class of agent for another, so-called “drug holidays”. In fact, a recent study has suggested a tapering schedule of sedative agents and opioids may be associated with worsened withdrawal syndrome; this may be due to patients on tapering doses receiving a greater total dose of the drug in question. Common sense dictates that we should use the smallest possible doses of these agents in an attempt to prevent withdrawal syndrome from occurring.

**PROCEDURAL SEDATION**

The aims of procedural sedation in children are generally to allow the completion of a specific procedure with relief of anxiety and pain and reduction of excessive movement using therapeutic agents appropriate to the clinical circumstance. Current definitions describe a continuum of the depth of sedation ranging from “minimal sedation” or anxiolysis, through “moderate sedation/analgesia” and “deep sedation/analgesia” to “general anaesthesia”.

The precise strategy for procedural sedation in the PICU will depend on the procedure being contemplated and the patient. The cardiorespiratory stability of the patient, the pre-existing level of sedation and the degree of monitoring can all influence the strategy. Non-pharmacological interventions may be considered. Two particular pharmacological agents are more likely to be used in this setting; propofol and ketamine.

**Propofol**

Propofol (2,6-diisopropylphenol) is an intravenous sedative-hypnotic agent licensed for use in the induction and maintenance of anaesthesia in adults and children over the age of 1 month, and for the sedation of adults during critical illness. It is unrelated to barbiturate, steroid, imidazole or eugenol drugs. One of the most attractive properties of propofol is its rapid onset of action with hypnosis usually occurring within 40 seconds of an injection. It is rapidly taken up into brain tissue and works through a variety of mechanisms. The drug appears to work, at least partially, through the GABA<sub>A</sub> receptor pathway. A further appealing property of propofol is its very rapid recovery time once the drug is discontinued.

In 2001 the UK Medicines Control Agency and Committee on Safety of Medicines repeated advice that propofol was contraindicated in children aged 16 years and under when used as an infusion for sedation and was not recommended for procedural sedation in children. The reason for caution is that it has been associated during prolonged administration with the so-called propofol infusion syndrome characterised by acidosis, bradyarrhythmia and rhabdomyolysis. This complication is rare but frequently fatal and has been reported in at least 21 children and 14 adults. When propofol infusion syndrome occurs, fatty acid oxidation and mitochondrial activity is impaired with transient...
elevations in malonylcarnitine and CS-acylcarnitine.57

In a recent survey of PICUs in the UK and North America propofol was used for sedation during procedures by all 48 responding units. Among the UK units 35% reported that they would be less likely to use propofol for procedures than in the past, compared to 18% of North American units.58

Ketamine
Ketamine is a dissociative anaesthetic agent, structurally similar to phencyclidine, which produces a cataleptic trance-like state by apparently producing an electrophysiological dissociation between the limbic and thalamocortical systems.59 It is the only agent that confers high levels of both sedation and analgesia. It has a rapid onset of action and a short duration of action owing to its short redistribution half-life of five minutes; the elimination half-life is 130 minutes. Ketamine has its short redistribution half-life of five minutes; the half-life of both sedation and analgesia. It has a rapid onset of action and a short duration of action owing to its short redistribution half-life of five minutes; the elimination half-life is 130 minutes. Ketamine has several unique features that include producing virtually no central respiratory depression, the maintenance of airway reflexes and bronchodilation. In addition, functional residual capacity, minute ventilation and tidal volume are unaffected following the administration of ketamine. It has fewer cardiac side effects than other sedative agents primarily because it tends to stimulate endogenous catecholamine release, producing increases in heart rate, blood pressure and cardiac output.

Green and colleagues have reported a retrospective study of 442 procedural sedation episodes using ketamine in 355 children on a PICU.60 Adequate sedation was noted in all but nine procedures (98%), complications were more common in those children who were not already intubated with 15 airway complications (5.4%) and 10 episodes of emesis (3.6%) in non-intubated patients.

COMPARATIVE STUDIES
Comparative studies of sedative agents for procedures in the PICU are hampered by the low incidence of serious adverse events. Many thousands of patients would need to be enrolled in prospective studies to establish any difference in mortality between two different regimes. Several authors have compared propofol with ketamine for procedural sedation; both agents appear to be safe and effective in this setting with a suggestion that transient cardiovascular and respiratory compromise is more likely following the administration of propofol, although faster wakening was generally seen with this agent.61-63

Funding: None.

Competing interests: None.

REFERENCES
Hutchinson-Gilford progeria syndrome

The Hutchinson-Gilford progeria syndrome is rare but it may provide some understanding of the mechanisms of normal ageing. A paper from the USA (Melissa A Meredith and colleagues. New England Journal of Medicine 2008;358:592–604; see also Perspective, ibid: 552–5) has provided detailed information about 15 children (almost half of all known patients worldwide).

The patients were unrelated, white children aged 1 year 6 months to 17 years 8 months; eight were girls. All had sclerotic skin, joint contractures, bone abnormalities, alopecia and growth impairment. Cardiovascular investigations showed worsening vascular function with age, with raised blood pressure, reduced vascular compliance, decreased ankle-brachial index and adventitial thickening. Many had dental and visual abnormalities. Previously undescribed features included raised platelet counts, prolonged prothrombin times, raised serum phosphorus concentrations, low frequency conductive hearing loss, and functional oral deficits.

Progeria results when a mutation of the lamin A gene (LMNA) results in the production of abnormal lamin A (progerin). Because people with the disease do not live to reproduce every case represents a new mutation. Progerin disrupts the structural integrity of the inner nuclear membranes. How that causes the progeria phenotype is not understood. Nevertheless, enough is known for trials of various agents that interfere with the actions of progerin to be proposed.

Other conditions associated with premature ageing include Werner’s and Cockayne’s syndromes.