

Sedation in intensive care patients

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Summary

Many critically ill patients require sedation in order to tolerate more invasive therapies, such as intubation and ventilation. The level of sedation should be assessed regularly and 'sedation holds' may reduce the duration of ventilation. The available drugs are discussed with emphasis on their advantages and disadvantages.

INTRODUCTION

Sedation is an essential component of the management of intensive care patients. It is required to relieve the discomfort and anxiety caused by procedures such as tracheal intubation, ventilation, suction and physiotherapy. It can also minimise agitation yet maximise rest and appropriate sleep. Analgesia is an almost universal requirement for the intensive care patient. Adequate sedation and analgesia ameliorates the metabolic response to surgery and trauma. Too much or too little sedation and analgesia can cause increased morbidity, for example over sedation can cause hypotension, prolonged recovery time, delayed weaning, gut ileus, DVT, nausea and immunosuppression; under sedation can cause hypertension, tachycardia, increased oxygen consumption, myocardial ischaemia, atelectasis, tracheal tube intolerance and infection.

Sedation in the ICU varies widely from producing complete unconsciousness and paralysis to being nursed awake yet comfortable. There are many components to the ideal regimen but key elements include recognition of pain, anxiolysis, amnesia, sleep and muscle relaxation.

Although the mainstay of therapy is pharmacological, other approaches are just as important:

1. Good communication with regular reassurance,
2. Environmental control such as temperature, humidity, lighting and noise,
3. Explanation prior to procedures,
4. Management of thirst, hunger, constipation, full bladder,
5. Variety for the patient - e.g. radio, visits from relatives, washing/shaving,
6. Appropriate diurnal variation - gives pattern to days.

ASSESSING THE LEVEL OF SEDATION

The dosage of commonly used sedative and analgesic drugs varies widely between patients because of variations in pharmacokinetics and pharmacodynamics.

A valid method for monitoring sedation would allow sedation to be tailored to the individual.

Any scoring system needs to be simple, rapidly performed, non-invasive and, most importantly, reproducible. Physiological variables, serum concentrations of drugs and neurophysiological tools such as EEG, bispectral index and lower oesophageal contractility have all been used, but are expensive, unreliable and unavailable.

The best systems are clinically based. Commonly used ones include the Richmond Agitation Sedation Scale and the Ramsay Scale.

Table 1. *The Ramsay Scale - six levels of sedation are used.*

1. Anxious and agitated
2. Cooperative, orientated and tranquil
3. Responds to verbal commands only
4. Asleep but brisk response to loud auditory stimulus/light glabellar tap (to the forehead)
5. Asleep but sluggish response to loud auditory stimulus/light glabellar tap
6. Asleep, no response.

This should be completed hourly by the attending nurse, but can be reduced in frequency as the patient stabilizes. Levels 2 to 5 can be considered suitable for patient in the ICU.

An increase in the sedation score must prompt the physician to make a differential diagnosis between over sedation or neurological/biochemical disease.

As a rule, the aim for the majority of patients is for them to be sleepy, although easily rousable and hence cooperative. There is a definite trend and increasing body of evidence towards less sedation and more analgesia, with daily sedation holds and spontaneous breathing trials.¹ It is preferable to allow the patient to breathe as soon as possible with triggered ventilation, such as pressure support. Ventilators are becoming increasingly sophisticated to allow a patient to

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Table 2. The Richmond Agitation Sedation Scale - the score ranges from +4 to -5.

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes, catheters, aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening >10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unrousable	No response to voice or physical stimulation

This should be repeated regularly and a suggested aim should be for a score of 0 to -1.

synchronise with the ventilator. Deep sedation with or without paralysis is reserved for severe head injury, critical oxygenation (reduces work of breathing and improves chest compliance) and diseases such as tetanus.

DRUGS USED IN SEDATION

The ideal sedative agent should possess the following qualities:

- Both sedative AND analgesic
- Minimal cardiovascular side effects
- Controllable respiratory side effects
- Rapid onset/offset of action
- No accumulation in renal/hepatic dysfunction
- Inactive metabolites
- Cheap
- No interactions with other ICU drugs.

Such a drug does not exist and therefore typically drug combinations are required. Sedative drugs may be given as boluses or infusions. As a rule, infusions for maintenance are preferable, with boluses for procedures, although continuous infusion results in higher cumulative doses.

Benzodiazepines

These are particularly useful because they are anxiolytic, anticonvulsant, amnesic and provide some muscle relaxation in addition to their hypnotic effect. Their effects are mediated by depressing the excitability of the limbic system, via reversible binding at the gamma aminobutyric acid (GABA)-benzodiazepine receptor complex. They have minimal cardiorespiratory depressant effects and are also synergistic with opioids. However rapid bolus doses can cause both hypotension and respiratory arrest. They are all metabolised in the liver. The common drugs used in this class are diazepam, midazolam and lorazepam. Diazepam use has decreased because of concern about its active metabolites (especially nor-desmethyldiazepam), which has a long half

life and can accumulate, particularly in the elderly and patients with hepatic impairment. It is safe to give in single boluses, if given sensibly.

Midazolam is water soluble at pH 4, yet fat soluble at pH 7, thus avoiding the unnecessary solvents required with the other two drugs and hence causing less irritation at the injection site. It has three metabolites, one of which (1-hydroxymidazolam) can accumulate in the critically ill. The normal elimination half life is 2 hours but can be as long as a few days in the long term sedated, critically ill patient.

Lorazepam undergoes glucuronidation and has metabolites that are thought to be inactive. Overdose or accumulation can be reversed by flumazenil, the benzodiazepine receptor antagonist. It should be given in small aliquots as large doses can precipitate seizures. It has a half life of only 1 hour so may need to be given as an infusion. There is wide inter-patient variability in the potency, efficacy and pharmacokinetics of benzodiazepines, so the dose must be titrated to the level of sedation.

After long term administration the dose should be reduced gradually or a lower dose reinstated if there is withdrawal (symptoms include insomnia, anxiety, dysphoria and sweating.)

Propofol (2,6-diisopropylphenol)

The mode of action is via the GABA receptor, but at a different site to the benzodiazepines. It was first developed as an intravenous anaesthetic agent and has a rapid onset of action yet, because it is metabolised rapidly both hepatically and extra-hepatically, it is ideal for continuous infusion. Recovery usually occurs within 10 minutes but it can accumulate with prolonged use, particularly in the obese patient. It is solubilised as an emulsion and the formulation can cause thrombophlebitis and pain, so ideally it should be infused via a large or central vein. Prolonged infusions can lead to increased triglyceride and cholesterol levels and its use is not licensed in children because of associated deaths attributable to this fat load. A theoretical maximum recommended dose is thus $4\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ to avoid 'propofol infusion syndrome', a rare syndrome leading to cardiac failure, rhabdomyolysis, metabolic acidaemia and renal failure. It is often fatal, treatment is supportive but early recognition reduces mortality.

Disadvantages also include cardiorespiratory depression, particularly in the elderly, septic or hypovolaemic patient. Infusions may cause the urine to turn green.

Ketamine

Ketamine acts at the N-methyl-D-aspartate (NMDA) receptor. In sub-anaesthetic doses ketamine is sedative and also analgesic. However it is generally not used because of the rise in blood pressure, ICP and pulse rate that may result. It also causes hallucinations but these can be avoided if administered concomitantly with a benzodiazepine. It appears not to accumulate and sometimes has a role in severe asthma given its bronchodilatory properties.

Etomidate

Historically was used in ICU as an infusion but is now no longer used as it has been shown to cause adrenal suppression, even after a single dose.

Barbituates

These, for example thiopentone, have been used, especially in the management of patients with head injuries and seizure disorders. They cause significant cardiovascular depression and accumulate during infusions leading to prolonged recovery times. Thiopentone is still used occasionally in severely raised ICP to induce a 'barbituate coma', and in intractable seizure activity. Its effect can be titrated using EEG burst suppression.

Butyrophenones and phenothiazines

Strictly these are classed as major tranquillizers but they remain useful in ICU, particularly in agitated/delirious patients.

A 'sliding scale' of haloperidol may be particularly useful in a patient with delirium to promote calmness i.e. increasing doses if no effect after 15 minutes until the desired response is achieved. Haloperidol in particular causes minimal respiratory depression and has less alpha blocking tendency than chlorpromazine and hence less hypotension. Other side effects include prolongation of the QT interval (caution when given with erythromycin), extrapyramidal effects or neuroleptic malignant syndrome.

Clonidine

This is the most well known of the alpha-2 agonists but also has alpha-1 agonistic properties. A more specific agonist is dexmedetomidine but this is expensive and rarely available at present. It is particularly useful in patients with sympathetic overactivity, such as alcohol withdrawal and tetanus, as it inhibits catecholamine release. It is also synergistic with opioids and acts at the spinal cord to inhibit nociceptive inputs, thus imparting analgesia. It is contraindicated in hypovolaemia and can cause hypotension, bradycardia and dry mouth.

Chlormethiazole

This is a vitamin B derivative widely used for treatment of delirium tremens. It is not a respiratory depressant and is an anticonvulsant.

Chloral hydrate

This is used in paediatric intensive care as an adjunct, usually to a

benzodiazepine such as midazolam. It is metabolised in the liver to the active compound trichloroethanol. Metabolites can accumulate in renal dysfunction.

Volatile agents

Isoflurane has been used in concentrations of up to 0.6% and produces good long term sedation with minimal cardiorespiratory side effects and yet rapid awakening. Scavenging and pollution are a problem as is incorporating the vaporiser into the ventilator. Free fluoride ions from metabolised methoxyflurane can cause renal failure. More recently desflurane has been shown to be effective in sedation with rapid offset of effects.

DRUGS USED FOR ANALGESIA (in combination with sedation)

Opioids are the mainstay of treatment and possess sedative, antitussive (cough suppressant) and hypnotic effects, besides the obvious analgesic effects. They work at the opioid receptors, reclassified in the late 80's to OP1 (old delta), OP2 (old kappa), OP3 (old mu). Most of the recognised effects are mediated via the OP3 receptor. Undesirable effects include gastrointestinal stasis and respiratory depression. Newer opioids have fewer side effects and accumulate less. It is equally important however to remember other analgesic techniques such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and regional techniques (e.g. epidural infusions).

Morphine

This is a commonly used drug. All other opioids are measured against morphine, although some newer agents have specific advantages. The dose required for analgesia is very variable and it can be delivered as intermittent boluses (problems with peak and trough effects, but less accumulation) or as a continuous infusion.

Morphine is metabolised mostly in the liver to two main products, morphine-3-glucuronide and morphine-6-glucuronide (M-6-G). Both are excreted renally and accumulate in renal dysfunction. The M-6-G metabolite also has independent long lasting, sedative activity. Morphine has minimal cardiovascular side effects, unless given as a large bolus to hypovolaemic patients or secondary to histamine release. It can be used in renal failure as long as the dosing interval is increased or the infusion rate reduced. Normal duration of action after a single dose is about 2 hours. Care should be taken, as with all opioids, in hepatic failure.

Fentanyl

Fentanyl is a potent synthetic opioid. It is presented as a short acting opioid, with a rapid onset. After prolonged infusion the duration of action approaches that of morphine, although it does not accumulate in renal failure. It does not cause histamine release and is suitable for analgesia in the haemodynamically unstable patient.

Alfentanil

Alfentanil is one of the newer synthetic opioids and has an onset of action about five times faster than fentanyl, due to the small volume of distribution, but is less lipid soluble so is not prone to accumulation. The duration of action is about a third that of fentanyl and it too

is safe in renal failure. It has minimal cardiovascular effects and is a potent antitussive agent.

Remifentanil

Remifentanil possesses many of the qualities desired of the ideal ICU analgesic and sedative agent. Remifentanil is an ultra short acting opioid metabolised by non-specific tissue and blood esterases. It has a rapid onset of action and does not accumulate after infusion even in organ dysfunction. It enables predictable recovery, facilitating patient interaction and assessment and therefore enables a shorter weaning time and potentially a reduction in the time spent on mechanical ventilation.^{2,3} Many claim that remifentanil could help control ICU costs, by reducing the time spent in ICU.^{2,3} It is however very expensive and each intensive care unit would need to determine its own cost saving analysis.

DRUGS USED FOR MUSCULAR RELAXATION

In some patients muscle relaxation may be needed in addition to sedation and analgesia. Such indications include:

- Early resuscitation (including intubation)
- Refractory hypoxaemia e.g. ARDS - will decrease oxygen consumption and optimise chest wall compliance
- Raised intracranial pressure - stops coughing and patients resisting ventilation
- Tetanus
- During patient transfer
- To allow inverse ratio/prone ventilation

It is vital to remember that relaxants have no effect on conscious level or comfort and should be avoided if possible. There are no standard clinical techniques to monitor conscious level in the paralysed patient so it is necessary to give generous doses of sedative drugs. In the UK, use of relaxants has fallen from about 90% of patients in the 80s to 10% of patients in the 90s.

Some relaxants used in anaesthesia are less suitable for use in the ICU. Suxamethonium is predominantly used during emergency tracheal intubation, but the resultant rise in serum potassium must be expected which makes it inappropriate for use in cases of renal failure. Excessive potassium release also occurs after 48hrs in extensive burns and spinal cord injury.

Pancuronium is long acting, but it may cause tachycardia and accumulates in renal failure. Vecuronium is an analogue of the aminosteroid pancuronium, but causes minimal cardiovascular side effects. It is suitable for intubation and infusion. Atracurium is a benzyloquinolinium and is metabolised by ester hydrolysis and Hoffman (spontaneous) elimination. Its metabolites are inactive and it doesn't accumulate in renal or hepatic dysfunction. Histamine release occasionally occurs with boluses, but recovery occurs predictably within one hour, regardless of duration of infusion. The intubating dose is 0.5mg.kg⁻¹, infusion 4-12mcg.kg⁻¹.min⁻¹.

Monitoring should ideally be performed using a nerve stimulator (e.g. train-of-four count). Clinical monitoring such as cardiovascular reflexes to noxious stimuli should also be observed. Full 'surgical' relaxation may not be necessary.

Problems with relaxants

1. The patient may receive inadequate sedation and be aware. This can be checked by withdrawing muscle relaxants for a time to allow recovery of muscular function and assessment of sedation levels.
2. Accumulation (especially with aminosteroids) in acute renal failure.
3. Critical illness polyneuropathy and myopathy (esp. if steroids also used).
4. Tendency to over-sedate.
5. Enhanced paralysis from other common ICU problems such as hypokalaemia, aminoglycoside antibiotics, hypophosphataemia.

RECOMMENDATIONS

Non-ventilated patients

Pain should be titrated with opioids to the desired level. Cooperative patients may benefit from patient-controlled analgesia. Regional techniques in selected patients are ideal. Always use simple analgesics in combination, and consider other causes for pain e.g. full bladder.

Postoperative/short-term mechanical ventilation

If available, then a combination of remifentanil or alfentanil and propofol allows a rapid wake up, but is only beneficial if used for less than 72 hours. Sometimes the high costs of short acting agents can be offset against the higher hidden costs of delayed weaning/ prolonged ICU stay. Alternatively a benzodiazepine/morphine combination can be used.

Long term mechanical ventilation

There is little logic in using very short acting substances in these cases. Kress et al performed a randomised controlled trial that showed that daily interruption of sedative infusions reduced the duration of mechanical ventilation and intensive care stay in the critically ill. Infusions were interrupted until the patient was awake and could follow instructions or became agitated or uncomfortable.⁴

Morphine plus midazolam or propofol were the agents used and the daily wake up procedure helped prevent excessive administration of these agents. A policy of interruption of sedation should be considered in all patients every day.

In some centres a newer technique of sedation is employed - patient controlled sedation - using increments of propofol, as opposed to morphine/fentanyl that is usually used in patient controlled analgesia. This is a very effective technique in the awake, orientated patient. It minimises nursing time, is inherently safe and gives control to the patient. However, it does require specialised, expensive equipment and is unsuitable for the majority of ICU patients.

SUMMARY

Good sedation can be achieved with a simple combinations of drugs. Over sedation is widespread but use of sedation scoring and adequate nursing staff provision should reduce its frequency. Use of sedative drugs should be reviewed daily, just as we assess use of vasopressors and inotropes. Sedation should be prescribed on an individual basis as requirements vary widely and sometimes analgesia alone may suffice.

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APPENDIX - DRUG DOSE COMMENTS

Drug	Dose	Comments
Propofol	0.5-4mg.kg ⁻¹ .h ⁻¹ Bolus 5-50mg	Not licensed for children for ICU sedation Care in hypovolaemia. Rapid recovery
Midazolam	0.5-10mg.h ⁻¹ Bolus 2-4mg Paeds: 5mg.kg ⁻¹ dissolved in 50ml (1ml.h ⁻¹ = 100mcg.kg ⁻¹ .h ⁻¹) Infuse 1-2ml.h ⁻¹	Cheap. CVS stable. Good for prolonged sedation. May result in very prolonged sedation, particularly in the elderly
Morphine	1-5mg.h ⁻¹ . Bolus 2-5mg Paeds: 1mg.kg ⁻¹ added to 50ml 0.9% saline. Infuse at 1-4ml.h ⁻¹ (1ml.h ⁻¹ = 20mcg.kg ⁻¹ .h ⁻¹)	Accumulates esp. in renal failure. Histamine release
Fentanyl	1-3mcg.kg ⁻¹ .hr ⁻¹ Bolus 50-100mcg Paeds: 50mcg.ml ⁻¹ Infuse 0.3 - 0.5ml.h ⁻¹ (= 5-10mcg.kg ⁻¹ .h ⁻¹)	Less accumulation in renal failure Less histamine release
Alfentanil	1-5mg.h ⁻¹ Bolus 0.5-1mg to supplement	Short acting and little accumulation Expensive
Haloperidol	5-10mg bolus	Minimal effect on respiration
Ketamine	Bolus 1-2mg.kg ⁻¹ then infuse 10-45mcg.kg ⁻¹ .min ⁻¹	Beneficial in severe asthma (bronchodilator) CVS stable Emergence delirium
Thiopentone	50-250mg.h ⁻¹	Use in epilepsy/raised ICP Very prolonged wake up
Remifentanyl	Start at 0.1-0.15mcg.kg ⁻¹ .min ⁻¹ titrate to range of 0.05-0.6mcg.kg ⁻¹ .min ⁻¹	Rapid onset and offset, does not accumulate in organ failure. Expensive. Can cause bradycardia