

# Sedation in the intensive care unit

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## Key points

Over-sedation can increase time on ventilatory support, prolong ICU stay, and may precipitate unnecessary neurological investigations.

Sedation should be tailored to the individual needs of the patient. A combination of drugs is often required.

A continuous infusion of a benzodiazepine has been identified as an independent predictor of a longer duration of mechanical ventilation, stay in the intensive care unit and stay in hospital.

Sedation scores should be used to allow titration of drug administration.

The sedation 'holiday' strategy has been shown to decrease the duration of mechanical ventilation and length of stay in ICU.

## Principles of sedation

Sedation allows the depression of patients' awareness of the environment and reduction of their response to external stimulation. It plays a pivotal role in the care of the critically ill patient, and encompasses a wide spectrum of symptom control that will vary between patients, and among individuals throughout the course of their illnesses. Heavy sedation in critical care to facilitate endotracheal tube tolerance and ventilator synchronization, often with neuromuscular blocking agents, was routine until relatively recently. The modern ICU ventilator is equipped with a wide range of ventilatory modes and, with the addition of electronic flow triggering, synchronization problems have largely disappeared. The replacement of an endotracheal tube by a tracheostomy reduces the discomfort associated with an artificial airway and may often remove the need for sedation entirely. Thus, modern day sedation involves more than tube tolerance and is now focused on the multifactorial individual needs of the patient.

Critical illness can be a frightening experience for a variety of reasons, and adequate sedation may reduce this. Pain is a common problem and may be worsened by invasive and unpleasant procedures. Agitation is thought to occur at least once in 71% of patients in a medical-surgical ICU.

## Monitoring sedation

### Why is it important?

How much sedation is given, and for how long, is important in determining patient outcome as both over and under-sedation can have potentially deleterious consequences. Over-sedation can increase time on ventilatory support and prolong ICU duration of stay. Under-sedation can cause hyper-catabolism, immunosuppression, hypercoagulability, and increased sympathetic activity.<sup>1</sup> Haemodynamic responses as a measure of sedation are unreliable in the critically ill patient, hence the need for formal sedation scoring.

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## Scoring systems

### Clinical scoring systems

There are many clinical scoring systems in use within the UK; examples include the Ramsay, Addenbrookes, and the Bloomsbury scales (Table 1). Each of these gives a quantitative score to a clinical finding in the awake or asleep state. Concerns with clinical scoring systems include interpreter variability and a lack of clear discrimination between deeper levels of sedation.

### Instrumental measures of sedation

Instrumental tools provide another approach to monitoring sedation and avoid the interpreter variability of clinical scoring systems. There are two main techniques:

- (i) *Electroencephalograms (EEG)*: This requires specifically trained personnel and equipment and is thus not practical in the intensive care environment.
- (ii) *Bispectral index (BIS)*: This technique is mostly used to monitor depth of surgical anaesthesia in the operating theatre; it provides a quantitative value between 0 and 99. A BIS value of 0 equals EEG silence, near 100 is the expected value in a fully awake adult, and between 40 and 60 indicates a level recommended for general anaesthesia. BIS has also been investigated in critical care, and several studies have shown a good correlation between BIS and Ramsay scoring for a Ramsay Score of 1–5. However, at the deeper levels of sedation (Ramsay Score 6), the BIS value showed greater variability.<sup>1</sup>

## Non-pharmacological methods of aiding sedation

Ensuring patient comfort requires a multidisciplinary approach in addition to pharmacotherapy. This includes frequent communication and explanation to the patient by all staff directly

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**Table 1** The Bloomsbury sedation scale

Sedation score	
3	Agitated and restless
2	Awake and comfortable
1	Aware but calm
0	Roused by voice
-1	Roused by touch
-2	Roused by painful stimuli
-3	Unrousable
A	Natural sleep
P	Paralysed

involved in their care, both nursing and medical, and relatives. Physiotherapy plays an important role as prolonged immobility may be painful and this can be reduced by daily assessment and treatment. Basic needs such as feeding and hydration require addressing regularly to prevent the symptoms of hunger and thirst.<sup>2</sup>

## Pharmacological management

Drugs commonly used for sedation in ICU are listed in Table 2. The class of medication used needs to match the underlying cause of discomfort. In a ventilated patient, this is often multifactorial, and thus a combination of pharmacotherapy may be required. When considering combinations of drugs, knowledge of their context sensitive half-times is essential.

### I.V. anaesthetic agents

#### Propofol

Propofol is extensively used in the intensive care setting as a sedative. It has been shown to be more effective compared with midazolam with respect to quality of sedation, and shortening of time between termination of sedation and extubation. In some studies, this has equated to a shorter ICU stay;<sup>3</sup> however, in others, the duration of stay was the same.<sup>4</sup>

Propofol has a high clearance, and metabolism is mainly dependent on hepatic degradation to glucuronide metabolites, which are subsequently excreted into the urine. Significant accumulation of propofol does not occur after bolus doses or a continuous infusion.

Infusion should be titrated to response (range 0.5–6 mg kg<sup>-1</sup> h<sup>-1</sup>). Problems with propofol sedation include bradycardia, myocardial depression, reduced systemic vascular resistance, and green coloured urine.<sup>5</sup> Propofol infusion syndrome may follow prolonged use because of its high calorie content (900 cal litre<sup>-1</sup>). This consists of severe metabolic acidosis and muscle necrosis, probably due to impairment of oxidation of fatty acid chains and inhibition of oxidative phosphorylation in the mitochondria.<sup>6</sup> Because of this, propofol is not licensed for children <3 yr old. Hypertriglyceridaemia after propofol use has also been shown to produce artifactual reductions of *in vitro* arterial and mixed venous oxygen saturations.<sup>7</sup>

Propofol 2% provides an alternative means of sedation with a lower lipid content and total volume.

#### Thiopental

Thiopental is now only administered by continuous infusion in the management of refractory status epilepticus. It has a low clearance and, when given as an infusion, its metabolism may become linear (zero order) due to saturation of hepatic enzymes;<sup>5</sup> thus accumulation is a serious concern, and may lead to myocardial depression and immunosuppression.

#### Etomidate

Although possessing the best haemodynamic profile of all the induction agents, etomidate is not administered by infusion due to potential suppression of adrenocortical function via inhibition of 11 $\beta$ -hydroxylase. Its use as a sedative in ICU has been shown to increase mortality.

#### Ketamine

Ketamine is a phencyclidine derivative that antagonizes the excitatory neurotransmitter glutamate at NMDA receptors. It produces a state of dissociative anaesthesia, profound analgesia, and amnesia. It is also a potent bronchodilator. Ketamine is not commonly used as a sedative infusion due to sympathetic nervous system stimulation resulting in increased cardiac work and a rise in cerebral metabolic oxygen consumption. Hallucinations, delirium, nausea and vomiting frequently follow its use,<sup>5</sup> but it still has a role in the management of status asthmaticus.

**Table 2** Sedative agents commonly used in ICU

Class of drug	Examples	Advantages	Disadvantages
I.V. induction agents	Propofol	Reduced duration of ventilation compared with benzodiazepines; little significant accumulation	Bradycardia; decreased systemic vascular resistance; propofol infusion syndrome
Neuroleptic agents	Haloperidol; chlorpromazine	Neuroleptosis; profound sedation; minimal respiratory depression	Extrapyrimal signs; hypotension; Q-T prolongation
Benzodiazepines	Midazolam; lorazepam; diazepam	Anxiolysis; haemodynamic stability	Dependence; withdrawal agitation; active metabolites (midazolam, diazepam); long elimination half-life (diazepam)
Opioids	Morphine; fentanyl; alfentanil; remifentanil	Analgesia; anxiolysis	Respiratory depression; bradycardia; respiratory depression; hypotension; nausea; constipation
Alpha agonists	Clonidine	Analgesia; anxiolysis; minimal respiratory depression	Rebound hypertension; hypotension; bradycardia; elimination delayed in renal failure

## Neuroleptic agents

### Haloperidol

Haloperidol is an anti-psychotic that produces a state of neuroleptosis via central dopaminergic D<sub>2</sub> blockade. This state is characterized by diminished motor activity, anxiolysis, and indifference to the external environment.<sup>5</sup> Haloperidol is useful in the management of postoperative psychosis and delirium as it produces profound sedation with minimal respiratory depression. It is commonly administered by i.v. bolus doses of 1–2.5 mg. Concerns include extrapyramidal effects and hypotension from peripheral  $\alpha_1$ -receptor blockade. Cardiac monitoring is recommended as it may cause Q-T prolongation and an increased incidence of arrhythmias.<sup>8</sup> It is metabolized in the liver to products with minimal activity; only 1% is excreted unchanged in the urine.

### Chlorpromazine

Chlorpromazine has similar indications and mechanism of action as haloperidol. However, it also has antagonist effects at muscarinic, noradrenergic ( $\alpha_1$  and  $\alpha_2$ ), histaminergic (H<sub>1</sub>), and serotonergic (5-HT) receptors and inhibits norepinephrine uptake into sympathetic nerves. Thus, chlorpromazine has a much wider profile of possible adverse effects. It is less sedative than haloperidol with a greater incidence of respiratory depression, and is rarely administered in ICU.

## Benzodiazepines

Benzodiazepines produce sedation and hypnosis by modulating the effects of GABA, the main inhibitory neurotransmitter within the central nervous system. They bind to the GABA<sub>A</sub> ligand gated Cl<sup>-</sup> ion channel. Benzodiazepines may be administered as bolus doses or by continuous infusion. They cause less haemodynamic compromise than i.v. anaesthetic agents. Concerns with their use include dependence and withdrawal agitation.<sup>5</sup>

*Midazolam* is metabolized in the liver to active compounds. It has the highest clearance of the benzodiazepines rendering it most suitable as an infusion (0.04–0.2 mg kg<sup>-1</sup> h<sup>-1</sup>).<sup>8</sup> *Lorazepam* has inactive metabolites, but a lower clearance and longer elimination half-life than midazolam. It is often used as a bolus method of producing sedation (1–4 mg p.r.n.). *Diazepam* is metabolized in the liver to active compounds. It has the lowest clearance of the benzodiazepines and its half-life is greatly increased by use as an infusion. It is not commonly used in ICU for sedative purposes. It can be given orally (2 mg three times daily) or i.v. (5–10 mg up to four hourly).

## Opioids

Opioids are commonly used to provide analgesia, narcosis, and anxiolysis. Side-effects include respiratory depression, bradycardia, and hypotension secondary to histamine release. They stimulate the chemoreceptor trigger zone and may cause nausea and vomiting via 5HT<sub>3</sub> and dopamine receptors. Opioids also inhibit

**Table 3** Properties of opioids commonly used in ICU

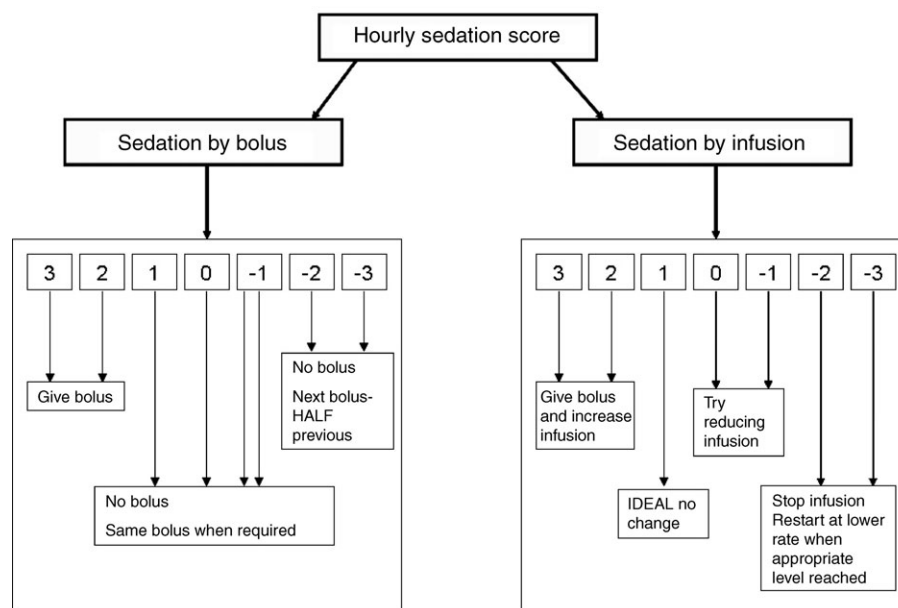
Opioid	Clearance ml kg <sup>-1</sup> min <sup>-1</sup>	Metabolism	Accumulation in renal failure
Morphine	16	30% is metabolized to morphine-6- glucuronide which is 13 times more potent than morphine and has a similar duration of action. Excreted in the urine	Yes
Fentanyl	13	In the liver to norfentanyl, which is rendered inactive by hydroxylation. Inactive metabolites are excreted in the urine	No
Alfentanil	6	In the liver by hydroxylation to noralfentanil, which is rendered inactive by conjugation. Excreted in the urine. Elimination delayed when given concurrently with midazolam as both metabolized by same enzyme	No
Remifentanil	40	Broken down by non-specific plasma and tissue esterases. Elimination half-life of 3–10 min independent of duration of infusion	No

peristalsis precipitating constipation.<sup>5</sup> The properties of opioids commonly used in ICU are listed in Table 3.

### Remifentanil

The use of the relatively new ultra-short-acting opioid remifentanil is increasing, and this merits further discussion. It is a potent pure  $\mu$  agonist and metabolized by non-specific blood and tissue esterases to remifentanil acid, which is essentially inactive; hence, its elimination is not dependent on normal hepatic or renal function. It has a highly predictable onset and offset, with a stable context sensitive half-time (3–10 min). Studies have shown a shorter duration of mechanical ventilation and quicker ICU discharge with remifentanil compared with other opioids.<sup>9</sup> This may offset the increased cost associated with the drug.

An infusion rate of 0.1–0.15  $\mu\text{g kg}^{-1} \text{ min}^{-1}$  may be started and adjusted at 5 min intervals by increments of 0.025  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ , according to response. If adequate sedation is not achieved at 0.2  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ , an additional sedative agent may be required.<sup>9</sup> The haemodynamic effects of remifentanil are similar to the other opioids, with a characteristic reduction of mean arterial pressure and heart rate; however, these effects become more significant above an infusion rate of 0.1  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ .<sup>11</sup> There are several case reports of acute tolerance and acute-onset withdrawal symptoms,<sup>10</sup> requiring patients to be re-sedated with remifentanil and weaned more gradually.



**Fig. 1** A typical sedation pathway, based on the Intensive Care Society Guidelines 1999.

Because of the very quick offset of analgesia, an alternative analgesic drug should be given before withdrawal of the infusion if pain is still likely.

### Clonidine and dexmedetomidine

Clonidine is an  $\alpha_2$ -agonist, which is increasingly used as a sedative in both mechanically and spontaneously breathing patients. It is particularly useful if agitation is a feature or after withdrawal of benzodiazepines or opioids. It may be administered by bolus doses (50–150  $\mu\text{g}$  t.d.s.) or as an infusion.

Clonidine acts via stimulation of  $\alpha_2$ -receptors in the lateral reticular nucleus of the medulla, resulting in reduced sympathetic outflow, causing profound analgesia and sedation without respiratory depression; hence, it is safe in spontaneously breathing/extubated patients. In addition to its central nervous system effects, it may also cause significant haemodynamic changes. This includes an initial rise in arterial pressure, which is later followed by a more prolonged fall. Bradycardia may occur due to a reduction in sympathetic tone and an increase in vagal tone. After abrupt withdrawal, acute rebound hypertensive crises have been reported. Clonidine has an elimination half-life of 8.5 h, 50% liver dependent, to inactive metabolites, and the rest is excreted into the urine; elimination is markedly decreased in renal failure.<sup>11</sup>

Dexmedetomidine is a more potent  $\alpha$ -agonist than clonidine; it is showing promise as a sedative agent in ICU and in paediatric anaesthesia, due to its shorter elimination half-life (2 h).

### Neuromuscular blocking agents

Neuromuscular blocking agents *do not* provide sedation, and are only occasionally used in critical care due to concerns about

chronic muscle weakness and the risk of paralysis without adequate sedation. Development of myopathy is directly related to duration of infusion.<sup>12</sup> Indications include:

- (i) invasive ventilation modes (e.g. inverse ratios, high pressures);
- (ii) control of ventilation in those with a high respiratory drive;
- (iii) reduction of oxygen consumption in critically hypoxaemic patients;
- (iv) control of raised intracranial pressure.

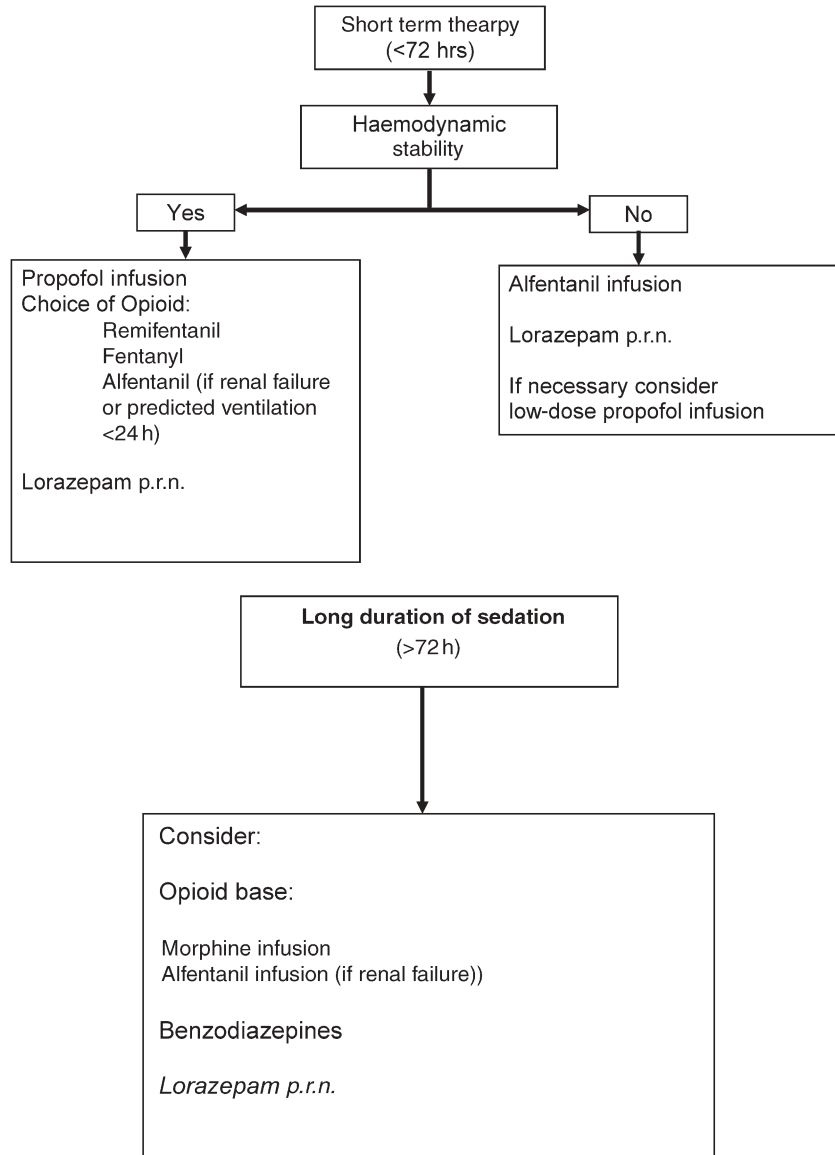
### Delivery of sedation

Sedative agents can be administered as boluses when required (usually as determined by the nurse looking after the patient), or by continuous infusion. The latter is most common, providing a constant level of sedation with less chance of intermittent agitation. However, a continuous infusion of sedation has been identified as an independent predictor of a longer duration of mechanical ventilation and a longer stay in the intensive care unit and in the hospital.<sup>13</sup>

Target sedation scores should be set and re-evaluated on a regular basis. This allows therapy to be titrated appropriately, to achieve the desired response, and should therefore prevent over and under-sedation as the clinical needs of the patient change.<sup>8</sup> Figure 1 shows a typical sedation pathway.

### Sedation holidays

A sedation holiday involves stopping the sedative infusions and allowing the patient to wake. The infusion should only be restarted once the patient is fully awake and obeying commands or until



**Fig. 2** An example of sedation protocol in clinical use.

they became uncomfortable or agitated and deemed to require the resumption of sedation. Ideally, this should be performed on a daily basis. This strategy has been shown to decrease the duration of mechanical ventilation and the length of stay in ICU, without increasing adverse events such as self-extubation.<sup>14</sup>

## Sleep on the ICU

Sleep is defined as a natural periodic state of rest for the mind and body, in which the eyes usually close and consciousness is completely or partially lost, so that there is a decrease in bodily movement and responsiveness to external stimuli. It is an important component in the recovery from critical illness and deprivation

may impair tissue repair and overall cellular immune function. However, sleep (quantity and quality) can be difficult to achieve in an ICU environment.

## Methods of aiding sleep

### Non-pharmacological methods

This involves modification of the patient's local environment and reduction of unnecessary noise. Sleep occurs best below 35 dB; a noise level of 80 dB will cause arousal from sleep. Lighting of the bed space to mimic the day–night orientation is helpful. Targeted music therapy can decrease heart rate, ventilatory frequency, myocardial oxygen demand, anxiety scores, and improve sleep.<sup>8</sup>

### Pharmacological methods

Benzodiazepines and benzodiazepine receptor agonists such as zopiclone are commonly used in non-intubated patients. They decrease sleep latency while increasing total sleep time, without affecting sleep architecture in stages 3 and 4 and REM sleep.<sup>8</sup> Concerns with drugs acting upon the benzodiazepine receptor include addiction, the 'morning hangover', and the possibility of rebound insomnia. Ramelteon, a melatonin receptor agonist, was approved by the Federal Drug Agency in 2005 for the long-term treatment of insomnia. It represents a novel treatment for the management of insomnia in the ICU environment and initial studies look promising, with a reduction in hangover effects.<sup>15</sup>

### Delirium

The recognition and management of delirium is important; it occurs in up to 80% of ICU patients during their admission. Old age and pre-existing cognitive dysfunction make it more likely and inappropriate or inadequate sedative therapy may exacerbate the symptoms. Delirium is characterized by an acutely fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation. It can be hyperactive or hypoactive. Hypoactive delirium, although not often recognized, has a worse prognosis and is characterized by psychomotor retardation manifested by a calm appearance, inattention, and decreased mobility. The hyperactive form presents with agitation, combative behaviour, and progressive confusion, often despite sedative therapy.<sup>8</sup>

Neuroleptic agents are commonly used to manage delirium and thought to act by exerting a stabilizing effect on cerebral function, reducing hallucinations, delusions, and unstructured thought patterns. Haloperidol is used more often than chlorpromazine due to its safer pharmacodynamic profile.

### Accumulation of sedatives

Accumulation of the sedative drug or its active metabolites is common, especially when hepatic and renal dysfunction occurs. This leads to over-sedation, greater haemodynamic instability, and prolonged duration of intubation and ICU stay. The action of anaesthetic induction agents is usually terminated by redistribution rather than clearance. Hence drugs with a low clearance given as a continuous infusion may accumulate leading to over-sedation.<sup>2</sup> Accumulation and over-sedation may be reduced or even avoided by the use of sedation scoring and sedation holidays.

### Sedation protocols

Sedation protocols should be standard in every critical care, and followed by nursing and medical staff. An example of a sedation protocol in clinical use is given in Figure 2. Such protocols should be regularly updated. Titration of individual patients' sedation throughout their ICU admission should reduce over-sedation and side-effects, and contribute to reduced duration of mechanical ventilation and length of stay.

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Please see multiple choice questions 9–11