Sedation and analgesia
Skills and techniques

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LEARNING OBJECTIVES

After studying this module on Sedation, you should be able to:

1. Outline an approach to sedation and relief of pain based on the patient's needs
2. Identify different techniques and routes of drug administration
3. Use appropriate monitoring tools and manage adverse drug effects
4. Modify interventions based on cost/benefit analyses

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DURATION 5 hours
INTRODUCTION

What is sedation?

The need for sedation is multifactorial. Appropriate analgesia is frequently the key requirement.

Sedation comes from the Latin sedare – to soothe. Nearly all critically ill patients will need some kind of 'soothing'. Consideration of the complexity of the Critical Care scenario allows appreciation of the diverse nature of a patient’s need for sedation.

Sedation is a broad term. It is often assumed to mean just hypnosis, but it is much more than this and may include:

- Pain relief and reduction of discomfort caused by intensive care technology, e.g. tubes and ventilators and the obligate posture of critically ill patients
- Relief from fear and anxiety
- The desire for a good night’s sleep
- Reduction of awareness (hypnosis)
- Reduction of stimulation and the consequent changes in arterial pressure, ventilation/PaCO₂, shivering, cough, posturing – all of which are potentially associated with increases in cerebral metabolic consumption and intracranial pressure, particularly in the neurological intensive care patient
- Control of delusional agitation/delirium.
1. IDENTIFYING PATIENTS’ NEEDS; APPROACH TO SEDATION AND PAIN RELIEF

Prior to making specific decisions regarding an individual patient’s sedation requirements, consider the following:

- Clearly define the individual patient's problem – need for analgesia, anxiolysis, antipsychosis, or any combination of these
- Determine if sedation is the primary requirement
- Estimate the period of time for which sedation will be required
- Administer the drug that has the best pharmacokinetic profile. This profile should be individualised in accordance with patient co-morbidities and primary disease (neurological, septic, cardiac), as well as medical vs postoperative, surgical ICU admission. Further details of these universally applicable recommendations are contained in the following references. See the guidelines on the SCCM website, http://www.sccm.org [LearnICU/Administration/Administrative Guidelines].

Amongst the various factors leading to the need for sedation/analgesia in individual patients, the following are the most common:

**Relief of pain**

This is one of the commonest causes of patient distress. Pain may be suffered as a consequence of surgery, trauma or inflammation, such as pleurisy, peritonitis or pericarditis. Pain can be relieved by administering analgesics.
Other causes of discomfort include the presence of a tracheal tube, full bladder or bowel, chest tubes and immobility. Hypnotic drugs must not be used in an attempt to reduce pain because any periods of consciousness the patient has are then filled with pain. Recent data suggest that ICU patients often suffer from inadequate analgesia. Daily pain assessment and optimisation of analgesia may reduce the duration of ventilation and ICU length of stay.


**Mechanical ventilation**

Mechanically ventilated patients may have additional needs, e.g. An antitussive effect to help the patient to tolerate the presence of a tracheal tube and tracheal suction without prolonged periods of coughing.

- Tolerance of mechanical ventilation. Although modern ventilators that allow synchronised spontaneous breathing have reduced the need for sedation, some is usually needed, particularly following initiation of assisted ventilation.

**Note** Keep these factors in mind as you consider the sedation requirements of an individual patient. Remember that these requirements, perhaps more than any other facet of critical care, are subject to wide individual variation.

**Fear and anxiety**

The relief of fear and anxiety at an early stage is a key therapeutic objective.

- Many critically ill patients are convinced they are going to die. Reassurance from the patient's caregiver may help to overcome this fear. Discussions at the patient's bedside should avoid issues such as withdrawal of futile, invasive treatment, outcomes and possible diagnosis of cancer to prevent unnecessary distress.
• Some critically ill patients will be sufficiently alert to be worried about the impact of their illness on their family and other loved ones. Involvement of social services may be helpful in this respect.
• If the patient has come into an ICU following an accident, other members of the family may have been injured or even killed. Some patients will therefore be bereaved and may benefit from professional counselling.
• Many patients cannot talk and are unable to write legibly. The inability to communicate increases frustration and may add to the patient’s fear and anxiety.
• The unfamiliar environment of the ICU combined with the presence of numerous strangers is a further source of stress.

It is important to remember that a sympathetic and thorough explanation, perhaps combined with a visit from a family member, may be all that is required. See the following references for further information.


PACT module on Communication skills

A good night’s sleep

Patients treated in ICUs are constantly being disturbed. Not only are many mechanically ventilated but, there is also the need to attend to bodily functions such as eye, mouth and skin care. In addition, alarms are disruptive and can provoke considerable anxiety. As a consequence sleep deprivation is common and the normal day/night sleep cycle is almost universally disturbed. This disruption can be reduced by darkening the room at night, maximising quiet periods and minimising direct patient disturbance at night. Although the ICU environment itself contributes greatly towards sleep disruption, other factors including drugs e.g. sedatives, analgesics, corticosteroids, phenytoin, clonidine, beta-blockers also interfere with normal sleep patterns. Efforts aimed at maintaining adequate sleep are essential since sleep deprivation predisposes to delirium, which in turn, may independently increase morbidity and mortality.

We all need a good night's sleep. Think about how you feel after a busy night on call; imagine what it must be like to be awake night after night. Before starting night sedation, however, it is important to ask the patient whether they feel tired. It is a common belief that everyone needs eight hours sleep every night. For some four hours may be sufficient, even when they are ill.

**Amnesia**

Amnesia is often an unintended consequence of administering hypnotic drugs. Previously, amnesia was thought to be harmless, but it is now recognised as being potentially harmful to the long-term psychological well-being of the patient. Amnesia is rarely desirable, indeed some patients may find being able to remember their time in intensive care helpful.

The occurrence of neuro-cognitive disorders/post-traumatic stress disorders after ICU has been linked to (deep) incl. lorazepam/midazolam sedation and to diminished memory of ICU, particularly if memory is absent or delusional in character. See link to [ESICM Flash Conference: E Azoulay ‘Post-ICU cognitive dysfunction’ ESICM congress, Vienna 2009](#).

In the following references you will find further information about the relationship between memories of intensive care and the level of anxiety and incidence of post-traumatic stress disorder-related symptoms after discharge.

Humanitarian concerns

It is an easy option to sedate patients pharmacologically. Attending to your patient's humanitarian needs, however, is of paramount importance. Drugs should be seen as complementing not substituting for this aspect of patient care.

The following points should be borne in mind:

- Environment – day and night pattern of activities in cheerful, pleasant and welcoming surroundings – attempting as far as possible to promote a near-normal atmosphere and minimise the hospital/institutional ambience.

- Reassurance – kind words may relieve anxiety.

- Explanation – communication should be both informative and enlightening.

- Careless discussion in front of an awake patient can cause anxiety.

- Full bladder, distended bowels, and other irritants such as an itch from a plaster cast are all potent causes of discomfort in the critically ill patient that are best relieved by dealing with the cause, rather than giving sedative drugs.
• In comatose patients – flexed elbows and scheduled passive mobilisation with change of position is important.

• A quiet darkened room with the television or music system turned off, if necessary combined with ear-plugs and an eye-shade, will sometimes provide the patient with a better night's sleep than a hypnotic.

• A daily plan for the patient a day in advance, even if this only includes simple activities such as washing, watching television and a visit from relatives. Nothing is more demoralising than waking up to a day of interminable emptiness and uncertainty.

• During recovery from prolonged critical illness, attempts should be made to restore to the patient some degree of self-control over his or her immediate environment. This should include psychosocial aspects e.g. in some countries this might include alcoholic drinks as appetite stimulants.

• Efforts to maintain physiological circadian rhythm (room with a window, normal environmental light) may improve quality of sleep thereby reducing sleep deprivation and the risk of delirium.

You will wish to carefully consider all these points and their possible importance in individual patient care before rushing to the drug cupboard.

**NOTE** Sedative practice in the ICU is constantly evolving. Clarification of the needs of individual patients and increased awareness of the adverse effects of sedative drugs are increasingly appreciated as being relevant.

**Q. Why is it important for an ICU to have an agreed 'sedation policy'?**

A. Sedation policies help to ensure that the correct drug is given to the right patient, at the right time and in the right dose. In addition, they promote the efficient utilisation of resources. As with all 'policies' for managing the critically ill, they need to be applied intelligently.

**Q. Why is it important to determine and respond to individual patients' views on their needs for sedation/analgesia? How would you ensure this happens?**

A. Sedation and analgesia are given primarily to maintain patient comfort. During conscious sedation, titration of medication can be managed via direct patient feedback. Deeper levels of sedation are sometimes required to optimise patient management; specific sedation scales are typically used to titrate sedative dose. Patient surveys following transfer from the ICU can be used to evaluate the success of ICU pain management and anxiolysis protocols.
Q. A patient's needs for sedation will vary from time to time. Consider six possible factors that might account for such variation.

A.
- Changes in the patient's illness severity
- Need for further surgery
- Changes in the mode of ventilatory support
- Tolerance to drugs
- Changes in renal and liver function resulting in altered drug elimination
- Toxicity of the sedative agent, or its solvent
- Need for patient transfer (e.g. CT scan).

In the next ten patients under your care in the ICU, determine what changes in the sedative regime are required to accommodate the factors mentioned above.

Target-based sedation and analgesia


The use of a structured approach to sedation management, including guidelines, protocols, and algorithms can promote evidence-based care, reduce variation in clinical practice, and systematically reduce the likelihood of excessive and/or prolonged sedation. Many published sedation protocols have been tested in controlled clinical trials, often demonstrating benefits such as shorter duration of mechanical ventilation, reduced ICU length of stay, and/or superior sedation management compared to non-protocol based care. Implementation of sedation algorithms in ICUs is a challenging process for which sufficient resources must be allocated.

Implementation of protocols for targeted sedation

Continuous infusion sedation (CIS) is an independent risk factor for longer duration of mechanical ventilation and longer ICU length of stay. Daily interruption of sedation (DIS) with re-titration to minimise prolonged sedative effects is therefore recommended. DIS can be coupled with a daily spontaneous breathing trial. Use of sedation algorithm or protocol is essential. Important components include choice of sedatives and analgesics, tools to measure pain, agitation, sedation and patient–ventilator synchrony, and protocol design. Principles for developing and implementing protocolised sedation management can be summarised as follows:
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- Perform multidisciplinary development and implementation
- Establish treatment goals and specific targets that are frequently re-evaluated
- Measure key components (pain, agitation, sedation) using validated scales
- Select medications based on key characteristics and evidence
- Incorporate important patient considerations in selection of medication and management, including safety screening for at-risk populations
- Design the protocol to prevent over-sedation yet control pain and agitation
- Promote multidisciplinary acceptance and integration into routine care
- Institute daily interruption of sedation and analgesia, and emphasise the importance of intermittent use of sedatives and analgesics.

**Note** Although daily interruption of sedation has been demonstrated to be of benefit in certain ICU situations, it is not necessarily applicable for universal use e.g. in patients with intracranial hypertension. See Task 2 on daily interruption of sedation (DIS).

Use of a sedation algorithm is associated with shorter duration of mechanical ventilation, and/or shorter ICU length of stay. Other benefits include more ‘on-target’ sedation, less pain, reduced direct costs or medication use, less patient–ventilator asynchrony, and decreased incidence of ventilator-associated pneumonia.


(http://www.sciencedirect.com/science/article/B7RMB-4WN9T8P-8/2/10e4453105326c45b0af595acff05d3)

**Drugs**

Drugs, carefully considered and regularly reviewed, play a vital role. In most instances and particularly on admission to ICU, patients will require some form of pharmacological intervention to help them cope with pain, anxiety or sleeplessness.

You may find the following texts of particular value in this connection:
Although there are two broad categories of drugs: sedatives and analgesics, it is clear that there is considerable overlap between the two. The analgesic, morphine, for example, causes sedation while the relief of agitation with a drug such as clonidine may reduce pain. Some of the overlapping effects of drugs are illustrated below.

Note: in figure below, new short-acting alpha-2 agonists (i.e. dexmedetomidine) are already available in the US and should soon become available in many European countries.

**Hypnotic drugs**


Many of the sedative or hypnotic agents used in intensive care are also used in anaesthetic practice. Although valuable insight into their actions can be obtained in the operating room, they may behave differently when used in the critically ill.

A dose that is suitable for use in a fit and healthy patient needing anaesthesia may be dangerous in a critically ill patient of similar age, height and weight.
Some of the hypnotic agents currently available are listed below, together with selected properties and metabolic actions.

**Benzodiazepines**

Benzodiazepines are particularly effective for relieving anxiety and producing amnesia and hypnosis. Their effects are mediated by depressing the excitability of the limbic system through reversible binding at the gamma aminobutyric acid (GABA)-benzodiazepine receptor complex. They have minor muscle relaxant properties that are mediated by the glycine receptors in spinal and supraspinal regions. All produce some degree of cardiovascular and respiratory depression.

The range of available benzodiazepines includes the relatively old drug, diazepam, and the much more commonly used midazolam.

**Midazolam**

Midazolam is water soluble at pH 4 and fat soluble at pH 7. It has three principal metabolites, 1-hydroxymidazolam (having one-fortieth of the activity of the parent drug), 4-hydroxymidazolam, and 1,4-hydroxymidazolam. In the critically ill patient the 1-hydroxy metabolite may accumulate. The normal elimination half-life is two hours but may increase to 24 hours in the critically ill. A special caution should be applied in the use of midazolam due to its propensity to induce tachyphylaxis and withdrawal syndrome. This is particularly true in children. The risk for accumulation and prolonged sedation is higher in patients with kidney or liver failure.

Q. Do special solvents present difficulties? Explain your answer.

A. Many drugs have to be dissolved in solvents other than water. When large amounts are given to patients, especially those with liver or renal failure, these solvents can accumulate and cause toxicity. For further information read Task 5.
Lorazepam

This drug has a half-life of approximately 14 hours. Because lorazepam metabolites are glucuronides they are considered to be inactive. Glucuronidation pathways are spared in liver disease and lorazepam may therefore be useful in such conditions. However, it is solubilised in propylene glycol and toxicity may arise if the infusion is prolonged or delivered at high doses. Thus repeated intravenous boluses are preferred to continuous infusion when possible. Lorazepam has found favour as an alternative to midazolam, particularly in North America. However, recent studies suggest that lorazepam (and therefore probably other benzodiazepines) is an independent risk factor for delirium in mechanically ventilated patients.


Diazepam

This drug has fallen into disuse because of concern about its long-acting metabolites. One in particular (nor desmethyl diazepam) has a longer elimination half-life than the parent drug. Being lipid soluble, diazepam has to be administered in a special solvent e.g. propylene glycol (which is an irritant) or soya bean extract. This agent is no longer recommended in general critical care practice but may have a role in neuro-critical care where its pharmacokinetic properties may not, in some patients, be considered to add to the weaning time and may attenuate withdrawal symptoms. Daily interruption of sedation (DIS – see Task 2) protocols may be utilised to limit oversedation.

Q. Why does prolonged sedation matter?

A. Unexpected and prolonged sedation is potentially dangerous. The duration of mechanical ventilation, the risk of organ failure and the incidence of tracheostomy are all increased. Unnecessary investigations, such as a head CT may be performed. ICU stay is prolonged and costs are increased. For further information read Task 5.

Q. What is the relationship between the half-life of a sedative agent and duration of effect?

A. Half-life is a pharmacokinetic term, while duration of action refers to the pharmacodynamics of a drug effect.

The American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) recommend propofol or midazolam for short-term sedation use. For further details read:


The following table is a guide to dosage of these three agents for longer term sedation in critically ill adults.

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Midazolam</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent bolus dose</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>Continuous infusion rate</td>
<td>2-10 mg/h</td>
<td>2-10 mg/h</td>
<td>2-4 mg/h</td>
</tr>
</tbody>
</table>

**Benzodiazepine antagonists**

**Flumazenil**

Flumazenil is a benzodiazepine antagonist with high affinity for, but no activity at the benzodiazepine receptor. Its half-life (approximately 60 minutes) is shorter than that of midazolam and lorazepam, and reversal of sedation (which can be abrupt) will be followed by resedation unless further doses are administered or flumazenil is given by infusion.

The IV dose starts at 0.2–1 mg, which is titrated to patient response. Flumazenil can cause benzodiazepine withdrawal and may induce seizures so it should be used with caution and is contraindicated in neurological intensive care patients especially in those at risk of seizure and with measured or suspected intracranial hypertension. Any neurological examination in patients receiving benzodiazepines should await drug washout as a clinical exam undertaken while the patient is under the influence of flumazenil may be distorted and hazardous. For further reading on this subject see:
Propofol

This intravenous anaesthetic agent also acts on the gamma aminobutyric acid (GABA) receptor. Propofol has cardiorespiratory depressant effects and may produce significant hypotension in hypovolaemic or septic patients. It is made soluble in soya bean extract. The potential for this solubilising agent to cause harm is described under solvents in Task 5.

The effects of propofol start and end quickly. Metabolised mostly by the liver, propofol metabolites are inactive. Special caution is warranted during hypothermia and in any condition of splanchnic hypoperfusion. In such conditions the rate of hepatic metabolism declines with the resultant risk of increased serum concentrations.

There are probably also significant extra hepatic sites of metabolism. The drug is usually given by infusion (maximum rate 4 mg/kg/h) but its use for long-term sedation (over 48hrs) is generally not recommended.

Propofol is particularly suitable for neurological intensive care patients. It is recommended as a first-line sedative after neurotrauma within the Brain Trauma Foundation guidelines.

Check your national regulatory authority or the European Medicines Agency (www.ema.europa.eu) for specific advice on the regulatory limit to infusion therapy in your jurisdiction

**Ketamine**

Ketamine is an anaesthetic agent similar in structure to phencyclidine. Its effects are mediated by N-methyl-D-aspartate (NMDA) receptor stimulation. Because it releases catecholamines, ketamine causes an increase in heart rate and arterial blood pressure in normal patients. This may not occur in the critically ill. Ketamine increases cerebral blood flow and metabolism and may thus raise intracranial pressure. Ketamine is also a bronchodilator and has been used in the treatment of severe acute asthma. Because one of its major adverse effects is nightmares, ketamine should always be combined with a benzodiazepine.

The dose is 25–50 mg as an intravenous bolus with an infusion rate of 10–30 mg/h. When given as an infusion it may be combined with midazolam in a 10:1 mixture (ketamine:midazolam).


**Thiopental (Thiopentone)**

Thiopental is a barbiturate developed as an anaesthetic induction agent, in which context it appears to be short acting because of redistribution into fatty tissue. Clearance, however, is by hepatic metabolism, and when given by prolonged infusion thiopental will accumulate, resulting in prolonged recovery, particularly in patients with impaired liver function. Immune suppression is also possible.

Thiopental is rarely used in intensive care, but may be considered for patients receiving mechanical ventilation who are difficult to sedate with other agents, or as a second line therapy for refractory intracranial hypertension. Thiopental is also an extremely effective anticonvulsant and can be given as a small (25 mg) bolus for the

*Always consider alternative drugs (and alternatives to drugs)*
treatment of refractory seizures. However, an infusion is preferred for sedation as a bolus given to critically ill patients may produce significant hypotension. Hypnotic effects are mediated through the GABA receptor at the barbiturate binding site. The usual dose by infusion is 2–5 mg/kg/h, with careful monitoring and reduction of dose with time.

Measuring plasma concentration of thiopental may be misleading, because the receptor concentration may be very different. However, a high plasma concentration usually indicates that a significant amount of the drug is bound to the receptor.

**Alpha-2 agonists**


Several alpha-2 agonists are available or being investigated. Clonidine is currently available in Europe. It is useful in patients suffering from withdrawal symptoms after discontinuation of continuous opioid infusions (usually fentanyl) for example.

Dexmedetomidine is a newer agent, licensed for use in the USA. It is a more selective alpha-2 agonist than clonidine, which is only a partial alpha-2 agonist and has significant alpha-1 agonist effects. Compared to clonidine, dexmedetomidine is eight times more potent. In addition, by comparison with other drugs, patients sedated with dexmedetomidine can be more easily roused, without being startled.

Further advantages of alpha-2 agonists include the ability to relieve anxiety and agitation and promote analgesia without clinically significant respiratory depression. Dexmedetomidine can also be used in unintubated surgical patients as a sole sedative agent in combination with other analgesics and during elective awake neurosurgical procedures. The amount of analgesic needed may be reduced. Both drugs may also have a place in the treatment of withdrawal syndromes.

Compared to lorazepam and midazolam, dexmedetomidine (0.2–1.4 mcg/kg/hr) may reduce the incidence of delirium and duration of mechanical ventilation. However, dexmedetomidine can cause bradycardia and hypotension and is expensive.


Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of
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Neuroleptics

Haloperidol is the most commonly used neuroleptic agent in the critically ill. It can be used to sedate an agitated patient with little risk of cardiorespiratory depression. The duration of action of haloperidol is about 4–8 hours and the dose is 2.5–5 mg repeated as necessary up to about 40 mg. Haloperidol may cause extra-pyramidal manifestations and, in addition, can prolong the Q-T interval on the ECG. Rarely haloperidol precipitates cardiac arrest. Formerly, droperidol was used as well, but has now been withdrawn in many countries.

**Note** Haloperidol is the preferred agent for treatment of delirium in the adult as recommended by the ACCM/SCCM. For further information on the practice parameters for intravenous analgesia and sedation see following reference.


As we have seen in the preceding section, there is a relatively wide choice of sedative agents for use in the critically ill. Most ICUs, however, tend to use a restricted number of such agents. Find out what are the three most commonly used sedatives in your own unit, what is the scientific evidence base for this choice and why alternatives are chosen for some patients. Determine in the next ten patients in your care the basis for selecting a particular agent (or combination of agents) and whether you have been consistent in your approach.

Q. For the following patients, which of the following agents would you use initially? They are all receiving an opioid for analgesia as well. (There may be more than one correct answer).

A. Benzodiazepine (intravenous)
B. Propofol
C. Ketamine
D. Thiopental
E. Alpha agonist  
F. Neuroleptics

1. A patient has a longer than expected femoro-popliteal bypass procedure. He comes to the ICU because of the long operation and a decrease in core temperature to 35.5 °C. The ICU course is expected to be short.

A. B. C. D. E. F.

A. The preferred option would be: B

2. A 21-year-old female has aspirated at induction of anaesthesia for a Caesarean section. Her chest X-ray shows diffuse pulmonary infiltrates and she needs an FiO2 of 1 with 10 cm H2O PEEP to maintain a PaO2 > 8 kPa (60 mmHg). Her heart rate is 140 bpm and her arterial blood pressure 80/50 mmHg. Because of a shortage of ICU beds she has been kept in theatre anaesthetised with isoflurane for the last six hours and has just arrived in the ICU.

A. B. C. D. E. F.

A. The preferred option would be: A

3. A 65-year-old male has developed multiple organ dysfunction after a perforated diverticulum resulting in faecal peritonitis. He also has acute respiratory distress syndrome. Currently he needs continuous veno-venous haemodiafiltration. Today he has become restless despite massive doses of midazolam. His serum is lipaemic. The struggling makes mechanical ventilation difficult, the increased venous pressure keeps stopping the haemofilter and the patient is at risk of pulling out his tracheal tube.

A. B. C. D. E. F.

A. The preferred options would be: E and F

4. A 28-year-old male is developing increasing intracranial pressure 2 days after a traumatic brain injury. Heart rate is 110 bpm, mean arterial pressure is 90 mm Hg and cerebral perfusion pressure is >60 mm Hg. The patient is on controlled-assisted ventilation but has some spontaneous breathing, which causes further increase of intracranial pressure.

A. B. C. D. E. F.

A. The preferred options would be: B

You should always be able to defend your choice of hypnotic agent.
**Analgesics**


Pain relief is clearly important. There are two major groups of relevant drugs – the opioid-based analgesics and the non-steroidal anti-inflammatory agents.

**Opioids**

The term opiate applies to the naturally occurring analgesics of this group. As more synthetic drugs are becoming available, the term opioid is now preferred. Morphine is the 'gold standard' to which all other opioids are compared.

Link to ESICM Flash Conference: Bernhard Walder, ‘Is morphine still the reference?’ ESICM congress, Vienna 2009

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The commonly used naturally occurring and synthetic opioids are shown below.

<table>
<thead>
<tr>
<th>Naturally occurring (opiates)</th>
<th>Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>pethidine</td>
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<tr>
<td>codeine</td>
<td>fentanyl</td>
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<tr>
<td></td>
<td>phenoperidine</td>
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<tr>
<td></td>
<td>sufentanil</td>
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<tr>
<td></td>
<td>alfentanil</td>
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<td></td>
<td>remifentanil</td>
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</tbody>
</table>
Opioid receptors

A classification of opioid receptors is shown in the table. Of particular importance are the μ-receptors that are responsible for inducing analgesia, as well as some of the important adverse effects of opioids such as respiratory depression.

Opioid receptor classification

<table>
<thead>
<tr>
<th>Opioid receptor classification</th>
<th>RECEPTOR</th>
<th>EFFECTS</th>
<th>AGONIST</th>
<th>ANTAGONIST</th>
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</thead>
<tbody>
<tr>
<td>OPs (μ)</td>
<td>Supraspinale analgesia</td>
<td>Morphine</td>
<td>Naloxone</td>
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<tr>
<td></td>
<td>Respiratory depression</td>
<td>Endorphin</td>
<td>Pentazocine</td>
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<td></td>
<td>Euphoria</td>
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<td></td>
<td>Physical dependence</td>
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<td></td>
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<tr>
<td>OPs (δ)</td>
<td>Modulation of μ activity</td>
<td>Leu-enkephalin</td>
<td>Naloxone</td>
<td></td>
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<tr>
<td></td>
<td>Supraspinale analgesia</td>
<td>Endorphin</td>
<td>Meptazocine</td>
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<tr>
<td></td>
<td>Supraspinale analgesia</td>
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<tr>
<td></td>
<td>Endorphin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPs (κ)</td>
<td>Spinal analgesia</td>
<td>Dynorphine</td>
<td>Naloxone</td>
<td></td>
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<tr>
<td></td>
<td>Respiratory depression</td>
<td>Pentazocine</td>
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<td></td>
<td>Sedation</td>
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<td>Miosis</td>
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</tbody>
</table>

In an attempt to unify opioid receptor classification, the International Union of Pharmacology (IUPHAR) has classified opioid receptors as OPs (μ), OPs (δ), OPs (κ). Recent advances in opioid pharmacology. Editor: BIA 1996:8:1–2. Note that this is a non-opioid system no longer considered an opioid receptor.

Morphine

The dose of morphine needed to produce analgesia is very variable and depends on many factors such as tolerance, as well as metabolic and excretory function. The usual dose for an adult undergoing mechanical ventilation is 2–5 mg as a bolus or by continuous infusion at a rate of 1–10 mg/h.

Morphine is metabolised mostly in the liver by the enzyme uridinosine diphosphate (UDP) glucuronyl-transferase system. There are two major metabolites – morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). M-3-G may be anti-analgesic whereas M-6-G is a potent analgesic. M-6-G has forty times the activity of morphine. Both metabolites may accumulate in renal failure.

Morphine is often the preferred agent for analgesia in the critically ill patient. However its onset time is slow. Consequently small boluses should be given several minutes before painful stimulation.

Pethidine (Meperidine)

Pethidine was the first synthetic opioid introduced into clinical practice. The bolus dose is 10 mg with an intravenous infusion rate of 10–50 mg/h. A major problem with pethidine is the active metabolite, norpethidine (normeperidine) which accumulates in renal failure and may cause seizures. For this reason pethidine is not recommended in the critically ill.
Many drugs have unexpected side effects. Opioids are no exception.

**Fentanyl**

Fentanyl is a potent synthetic opioid that penetrates membranes quickly and thus has a rapid onset of action. It is 75–200 times more potent than morphine. In patients needing mechanical ventilation the bolus dose is 50–100 µg and the infusion rate 100–200 µg/h. Duration of action is relatively short when first used at about 0.5–1 µg/kg/h. However, prolonged infusion may be complicated by accumulation, slow recovery and is associated with withdrawal symptoms. De-escalation dose of methadone could be a useful bridge in such phase.

Since fentanyl does not cause histamine release the SCCM/ACCM recommend fentanyl for analgesia in the haemodynamically unstable patient.

**Alfentanil**

Alfentanil is one of the newer synthetic opioids. Like all the others it is metabolised by the liver. Alfentanil has a short duration of action of about 15 minutes. The bolus dose is 250–500 µg with an infusion rate of up to 1–2 mg/h. Of all the opioids alfentanil is the least likely to produce active metabolites, although this is unproven.

Small bolus doses of alfentanil may help patients cope with short-lived, potentially disturbing nursing procedures e.g. turning to prevent pressure sores, an advantage in this context being the very rapid onset of action. However, if the patient is already on an opioid infusion then a bolus dose of the agent being infused may be given. Some opioids (for example morphine) have a long onset of action and need to be given well in advance of anticipated pain.

**Sufentanil**

Sufentanil is another synthetic opioid. It is usually given by continuous intravenous infusion at a rate of 0.3–0.09 µg/kg/h, a bolus dose of 1–2 µg/kg can also be given.

Fentanyl, alfentanil and sufentanil are synthetic opioids of the 4-anilidopiperidine group that are commonly used in the operating room. These opioids also undergo hepatic metabolism, and their continuous infusion can lead to accumulation as well as prolonged drug effects. This is especially true in critically ill patients, in whom drug clearance may be substantially reduced because of illness, organ dysfunction, or concomitant therapy. Therefore, their use is always accompanied by concerns regarding drug accumulation, which potentially can lead to prolonged respiratory depression and delayed and unpredictable recovery. When these opioids are compared, alfentanil is the drug with the most rapid onset of action and the
shortest duration of effect. However, alfentanil is a substrate for different cytochrome P450 3A enzymes, and its metabolism and offset of effect can underlie inter-individual variability due to polymorphic enzyme expression. Alfentanil can be markedly inhibited by different drugs, including antibiotics and antifungal medication. Thus, although single bolus injections of alfentanil are short acting, the effects of an infusion of alfentanil in ICU patients are much less predictable. Alfentanil is not the ideal short-acting opioid for use in the ICU.

Remifentanil

Remifentanil is a potent ultra short-acting selective µ-opioid receptor agonist and was first approved for use as an analgesic agent during induction and maintenance of general anaesthesia in 1996. In 2002 remifentanil received approval from the European Medicines Agency for provision of analgesia for a duration of up to three days in mechanically ventilated ICU patients, aged 18 years or older. Remifentanil differs from the other opioids in being metabolised by esterases that are widely distributed in all body tissues. Even during the anhepatic period of liver transplantation there is little change in pharmacokinetics, graphically illustrating the independence of this agent from normal routes of metabolism. The major metabolite, remifentanil acid, is a very weak opioid. Indeed, it is so weak that even in renal failure it is unlikely to exert any effect. The ability to provide intense analgesia with large doses of opioid means that less hypnotic agent is required. Patients are more awake and can move around and communicate with their caregivers. The dose is 6–15 (occasionally 30) µg/kg/h. Because of its unique pharmacokinetic profile, remifentanil is characterised by a rapid and uniform clearance and a highly predictable onset and offset of effect. Remifentanil has a terminal half-life of approximately 10 to 20 minutes, and its context-sensitive half-life is three to four minutes, regardless of the duration of infusion. Bolus doses are not usually recommended because of the risk of bradycardia and hypotension but have been studied – see below. It is not licensed for use in patients breathing spontaneously and because of its potency can cause sudden apnoea. Its unique characteristics make it suitable for patients in whom pain is a limitation for weaning. Once the causes of the patient’s pain are resolved, stopping remifentanil potentially helps a more rapid discontinuation of sedation.

In post neurosurgical patients in whom serial neurological examination is required, its short half-life make a rapid drug free examination possible.

It should be useful even in less severe patients with acute brain damage in whom monitoring e.g. intracranial pressure monitoring has not been applied and in whom a neurological examination is used to monitor the patient’s status.


Tramadol

Tramadol is an atypical opioid that is an agonist for µ-receptors. It is widely used in post-surgical ICUs. It can be given orally as well as intravenously.

Opioid antagonists

Two opioid antagonists are available, naloxone and doxapram, both working by different mechanisms.

Naloxone

This is a specific antagonist that binds to the µ-receptor. It completely abolishes the effects of all opioids at this site. The dose should be titrated carefully and slowly, 0.1 mg should be given intravenously every 3–4 minutes. Used without due caution, it can cause sudden reversal of analgesia, hypertension and tachycardia risking myocardial infarction or cerebrovascular accident in some patients. Acute arrhythmias and seizures have also been reported. In others it can cause an acute abstinence syndrome, especially those using opioids outside of hospital for recreational purposes.

Anecdote

A 21-year-old heroin abuser was admitted to the emergency department. He was unconscious, barely breathing and cyanosed. Tracheal intubation was immediately performed and ventilatory support given. As an opioid overdose was suspected 0.4 mg of naloxone was administered intravenously. He immediately sat up, pulled out his tracheal tube, started swearing and punching the staff. This 'large' dose of naloxone produced a sudden abstinence syndrome. In the critically ill, naloxone given incautiously will produce reversal of both respiratory depression AND analgesia. The pain may cause a sudden outpouring of catecholamines possibly resulting in arrhythmias including ventricular fibrillation.

Doxapram

This ‘physiological antagonist’ reverses opioid-induced respiratory depression with minimal effects on analgesia, by acting as a respiratory stimulant via the peripheral chemo-receptors. A bolus dose of 1–1.5 mg/kg can be used.
Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are rarely used in seriously ill patients because of their side effects (see figure below). These include:

- Anti-coagulant effect – due to interference with platelet function
- Renal impairment in patients who are hypovolaemic or septic (by inhibiting prostaglandin synthesis in response to pre-renal state in the kidney)
- Risk of gastrointestinal bleeding
- Acute bronchospasm.

Despite these risks in the occasional patient, such as the young adult after trauma or major surgery, NSAIDs can be useful. Diclofenac and ketorolac are commonly used. Ketorolac can be given intravenously and diclofenac rectally or, in certain jurisdictions, intravenously.

The dose of ketorolac is 10 mg six-hourly (for no more than two days) and diclofenac 25–50 mg eight-hourly.

Ibuprofen (400–600 mg eight-hourly enterally) is an acceptable alternative.

The adverse effects of non-steroidal anti-inflammatory drugs

Paracetamol (acetaminophen)

This is a non-opioid analgesic. It can be given (500 mg to 1 g) orally, rectally or intravenously to patients. The maximum dose in any one day is 4 g.

A wide variety of analgesics are available in most countries. Those most commonly used in European countries are described in this Task, although there are many more. Find out from your pharmacist:
- What drugs are available in your hospital that could be used once opioids have been discontinued or for less serious pain.
- Look these drugs up in your local formulary to find out exactly what they contain and recommendations for their use.
2. **TECHNIQUES AND ROUTES OF ADMINISTRATION**

In the critically ill, absorption via the gastrointestinal tract is often unreliable. Most drugs are given intravenously because absorption via the intramuscular or subcutaneous routes is also unpredictable.

Besides variable absorption the intramuscular route can be complicated by haematoma in coagulopathic patients, muscle wasting and the need for frequent injections.

**ANECDOTE**

Drugs absorbed via the GI tract may behave differently from those given intravenously because of first pass metabolism by the gut and liver. Venous access was proving difficult in a long stay patient on the intensive care unit. To preserve the veins that remained all her drugs were changed to the oral route and the intravenous lines removed. Morphine was being given for pain relief; this was changed to a slow release preparation. The following night, and for the next two nights until intravenous administration was restarted the patient experienced vivid nightmares. You might like to remember that Morpheus was the mythological god of dreams.

There are several ways of giving drugs intravenously.

**Bolus doses** – By this means the initial dose can be titrated to produce the desired effect which can then be maintained by repeat doses. Unnecessary administration is avoided. It does, however, have the disadvantage that the relatively rapid increase in the concentration of the drug may lead to adverse effects such as cardiorespiratory depression. Minimal equipment is needed, but intermittent bolus doses are more time-consuming for the nursing staff.

**ANECDOTE**

Several years ago a patient was admitted to the intensive care unit with an acute exacerbation of chronic obstructive pulmonary disease. She made good progress, but awoke one night and started to cough. This distressed her and she became hypoxic and hypercarbic as a consequence. At that time the ICU resident, who had heard about the new drug propofol but was uncertain how to use this agent, gave a bolus dose of 50 mg which calmed the patient down, stopped the coughing and straining, allowing the PaO₂ to increase and the PaCO₂ to decrease. When she awoke a few minutes later, the coughing gone, the only sedation she needed was some comforting words from the nurse at her bedside. No more sedatives were needed for six or seven hours. Remember even short-acting drugs do not always need to be given by infusion. More importantly, if you don't know a drug well, find out before using it!

The technique chosen for drug administration should be determined primarily by the needs of the patient.
**Continuous intravenous infusion.** This is the method most commonly used for sedative drugs. It is convenient for the staff and avoids sudden fluctuations in blood concentration. On the other hand, accumulation may be a problem, especially when drug elimination is adversely affected by critical illness. When the drug is stopped, prolonged coma may result. A further risk is infusion pump malfunction or misuse. In some 'critical incident' surveys, syringe pump 'errors' have been found to be very common. This can be avoided by regular monitoring and by allowing the patient to recover from the sedation each day.

**Daily interruption of sedative infusion**


An alternative sedation strategy that can be applied is daily interruption of sedative infusions (DIS). In 2000, Kress and coworkers showed that temporarily stopping sedative (midazolam or propofol) and analgesic (morphine) infusions until the patient was able to follow three or four simple tasks or was agitated led to significant reductions in duration of mechanical ventilation, shorter ICU length of stay and use of fewer diagnostic tests for unexplained changes in mental status.

There is evidence that sedative and analgesic agents should be interrupted once daily unless there is contraindication such as pain or patient distress or there is a raised ICP (see below) or ongoing neuromuscular blockade. Once the drugs are interrupted, the ICU team must be vigilant for evidence of patient distress, which may manifest as overt physical agitation, isolated haemodynamic lability (hypertension or tachycardia), or ventilator asynchrony. Providers are then encouraged to administer bolus drug dosing to control symptoms, and restart both sedative and analgesic drugs at half the previous infusion doses with subsequent titration to the desired depth of sedation. DIS can be combined with a spontaneous breathing trial. Close observation during DIS is required to reduce the risk of self-extubation and other consequences of agitation.

In patients with acute neurological disease at immediate risk of severe intracranial hypertension and or global or regional ischaemia, a scheduled neurological examination is not recommended. It should be done only if its benefits are believed to outweigh any potential for adverse effect. The level of intracranial pressure, pupil reactivity to light, CT findings and, importantly, the level of therapy applied to control ICP all are useful guides to plan daily sedation interruption.

In patients in whom intracranial pressure is controlled, and associated clinical and imaging findings suggest an improvement of initial damage, a daily interruption, or a progressive decline of infusion rate, is suggested. This should be useful to set new sedation levels once negative symptoms appear.
Daily wakening may not be suitable for neonates and young children. In these patients, continuous infusions of short-acting, more predictable agents such as remifentanil and propofol can be used.

Daily interruption of sedation (DIS) does not work in all ICUs. If your ICU is different, be aware of why.


If your ICU has regular 'critical incident' surveys find out the incidence of syringe pump 'errors'.

**Nurse-controlled analgesia** – a syringe of sedative or analgesic is push-button operated by the nurse when the patient is judged to need sedation or analgesia. A complex and expensive syringe pump is required. As the patient recovers, the pump can be programmed to allow patient-controlled analgesia.

PCAS/NCAS pumps offer good control of pain although they are expensive. Find out from your hospital stores or the manufacturers the cost of the pumps in your unit.

An approach to practice is to use sedative and analgesic drugs initially in small bolus doses and assess their effects. If the drug produces the desired effect for a reasonable period of time then management proceeds with repeated small intravenous bolus doses. If, however, the bolus doses need to be repeated frequently, then an intravenous infusion is started.
Target-controlled infusion (TCI). Although this is more established for anaesthesia, it is described for intensive care. See link to ESICM Flash Conference: Claude Martin, ‘Sedation (target controlled infusion)’ ESICM congress, Vienna 2009

Other routes of administration

Epidural infusion

Infusions of local analgesic agents often combined with opioids can give very effective analgesia e.g. in the case of fractured ribs or thoracic or abdominal wounds.

ANECDOYE

Local anaesthetics can be toxic if infused into the epidural space and not adequately eliminated. A patient who was involved in a road traffic accident and sustained fractured ribs on the left side resulting in a small flail segment had a thoracic epidural catheter placed and an infusion of bupivacaine started. This made the patient comfortable. On the third evening he became acutely confused. When seen by the doctor he was standing on his bed swinging his intravenous infusion round above his head! He thought the doctors were mistreating him and wanted to go to the police station to complain. His confusion was attributed to his bupivacaine and the epidural stopped (it had become disconnected anyway). After some gentle persuasion he sat down in his bed. Four hours later he was again rational. The epidural was restarted when his pain returned – at a lower dose.

Combination of drugs

Drugs may behave in different ways if given concurrently with another agent. Three different types of interaction are described. In the following description 1 equals the effect of a drug.

Additive effects \( 1+1=2 \)
Antagonistic effects \( 1+1=0 \)
Synergistic effects \( 1+1=3 \)

The phenomenon of synergy is commonly exploited when prescribing antibiotics. Recently, the importance of synergy has been appreciated with regard to drugs used for sedation.

Q. Name two synergistic combinations of sedative and analgesic drugs and explain why they are synergistic.
A. Propofol and midazolam, thiopental and midazolam. The mechanism for the synergy is thought to be at the GABA receptor. However, remember that propofol also acts on lipid membranes. The combination of safer drugs, for example midazolam with propofol, may help to reduce dosage of propofol which is a drug with a risky side effect profile.

Opioids and midazolam.
The mechanism for this is unknown.

**ANECDOYE**
An 18-year-old soldier was riding his motorcycle when a car emerged from a side road without stopping and hit him. He suffered a fractured tibia and a torn tibial artery. On arrival at hospital he went straight to the operating room where he underwent a long and bloody operation to repair his leg. For this reason he was transferred to the ICU to recover. There was, however, concern about the vascular repair. Although he was ready for tracheal extubation the surgeons asked that he be kept 'sedated' and on a ventilator in case he needed to return to the operating room urgently.

**Q. What action might you have taken in these circumstances?**

A. Normally, keeping young men sedated when they only have an isolated limb injury is difficult. In this patient, the critical care team used a synergistic combination of a low dose of propofol with intermittent bolus doses of midazolam. He was also given intermittent doses of morphine for pain relief.

**Q. Could he have had a morphine infusion? How fully does synergy between these drugs work?**

A. Arguably an infusion of morphine could have been used, since this patient was not at risk of accumulating the drug or the metabolite. Although morphine and midazolam are also synergistic, the additional combination does not further reduce the effective doses i.e. three-way synergy does not occur.
**3. NEUROMUSCULAR BLOCKADE**


The use of neuromuscular blockers (NMBs) in the ICU has decreased substantially in recent years. In the occasional patient, NMBs may be needed in addition to sedatives. Indications for the use of NMBs include:

- Resuscitation (including tracheal intubation)
- Ventilatory modes that are difficult for the patient to tolerate (such as high PEEP, prolonged I:E ratio)
- Extreme hypoxia/hypercarbia
- Raised intracranial pressure
- Ventilator/patient dyssynchrony when appropriate sedation and analgesia has failed (rare).

You may find the following texts of particular value in this connection:


**Warning:** Neuromuscular blockers are very potent and will stop a patient’s breathing. Before you give these drugs you must be competent at managing an airway and tracheal intubation. If you have not received this training, seek expert help. Resuscitation and specialist equipment must be available to deal with a (difficult) intubation. Before giving a neuromuscular blocker, the patient must be unconscious; hypnotic drugs are nearly always required.

The use of neuromuscular blockers in mechanically ventilated patients may be considered under two main headings:

- Cerebral protection – mainly by preventing increases in intracranial pressure caused by coughing and straining. This intervention makes
sense only as an acute intervention. Routine use of neuromuscular blockers is not necessary once the patient is appropriately sedated and with analgesia. Sometimes boluses of NMBs before and during transportation might increase its safety.

- Mechanical ventilation – of relevance in patients with lungs that are difficult to ventilate and who may need unusual ventilatory modes, such as reversed inspiratory–expiratory ratio. Neuromuscular blockers are not, however, always needed to tolerate reversed I:E ratio ventilation.

**Specific agents**

**Note** Muscle relaxant drugs should never be used alone! They should always be used in conjunction with sedatives and analgesics

A wide choice of neuromuscular blocking agents is available for use in the critically ill patient of which the following are most frequently used.

**Atracurium**

Atracurium undergoes spontaneous, ester hydrolysis (Hoffman degradation) to metabolites that are inactive at the neuromuscular junction. One metabolite, laudanosine, that accumulates in hepatic and renal failure, has been implicated in convulsions in animals, but never in man. Histamine release occasionally occurs with bolus administration, and tachyphylaxis may occur with prolonged administration. Recovery of neuromuscular transmission occurs predictably in less than one hour regardless of the duration of the infusion.

The dose of atracurium is 0.5 mg/kg for tracheal intubation and 0.5 mg/kg/h as an infusion. Atracurium may be indicated in those at risk of critical care weakness since the frequency of this complication appears to be less with this drug.

**Cisatracurium**

Atracurium is a racemic mixture of ten steroisomers. One of them, cisatracurium, makes up only 15% of the isomers but contributes 60% of the activity. It also releases much less (virtually none) histamine, resulting in greater cardiovascular stability. A pure preparation of this isomer is now being made available.

The dose of cisatracurium is initially 0.1 to 0.20 mg/kg with an infusion maintenance dose of 3 µg/kg/min or 0.18 mg/kg/h. Like atracurium it is eliminated by a Hoffman reaction and metabolism is independent of liver function.

**Pancuronium**

This is a neuromuscular blocking agent with a steroid structure. It can be given as a bolus dose of 0.1 mg/kg (which will last for one hour) or an infusion of 4–10 mg/h. The major disadvantage of pancuronium is that it can cause a tachycardia. It also accumulates in renal failure causing prolonged blockade. These complications and
the risk of critical care weakness have limited its use in many ICUs. However, the latest guidelines still recommend pancuronium unless vagolysis is contraindicated or there is renal or hepatic disease.

**Vecuronium**

Again this neuromuscular blocking agent has a steroid structure. In addition, it has an active metabolite – nor desacetyl vecuronium – that also accumulates in renal failure. The major advantage of vecuronium is haemodynamic stability – causing little change in heart rate or arterial blood pressure when given in the recommended dosage. The dose is 0.1 mg/kg as a bolus (which will last for about 45 min) and 0.8–2.0 µg/kg/min or 5–10 mg/h as an infusion.

**Rocuronium**

This latest steroidal neuromuscular blocking agent, like vecuronium, has marked cardiovascular stability. The other major advantage of this agent is a rapid onset of action which might make it useful for patients in whom rapid tracheal intubation is needed but in whom suxamethonium (succinylcholine) is contraindicated (see later). The dose of rocuronium is 35 mg as a bolus dose and 60–100 mg/h as an infusion. A bolus dose will last for about 45 min.

**Q. What is meant by Hoffman elimination and what is its clinical significance?**

A. This is a physiochemical reaction causing spontaneous breakdown of the drug. It is independent of enzyme action. The drug is thus reliably eliminated in hepatic and renal failure.

Further details can be found in:


**Anecdote**

A male patient aged 72 years was being treated in the ICU for a severe community acquired pneumonia. He needed a FiO₂ of 0.8 with 10 cm H₂O PEEP and an I:E ratio of 2 to 1 to maintain adequate oxygenation. At first he was given neuromuscular blockers (NMBs) to tolerate this pattern of ventilation. Because neuromuscular blockade was administered intermittently the team became aware that he tolerated the high PEEP levels and reversed I:E ratio for long periods between the doses of muscle relaxant and eventually, the team was able to stop the NMB completely. Sedation and analgesia, which he had been given for several days, while being given a neuromuscular blocker, could also soon be stopped.
The use of neuromuscular blockers varies widely between units and countries. In general their use has decreased and some units virtually never use these drugs except for tracheal intubation and surgical procedures.

**Suxamethonium (Succinylcholine)**

This differs from all the other neuromuscular blocking agents in being a short-acting depolarising agent. It is mostly used to achieve relaxation during rapid sequence tracheal intubation. It usually produces paralysis for about three minutes.

Because it causes depolarisation with muscle twitching, suxamethonium may be associated with the release of potassium. Normally, the increase is small but can be critical in certain categories of patients.

**Q. In what clinical situations might the administration of suxamethonium produce a large increase in plasma potassium to levels that could produce cardiac arrest?**

**A.**
- A spinal fracture or other denervation injury (including critical illness polyneuromyopathy)
- Burns (but not in the acute phase)
- Rhabdomyolysis
- Acute renal failure.

The usual dose of suxamethonium is 75–100 mg. It should be avoided in patients with raised intracranial pressure because the fasciculations may cause a further increase in intracranial pressure. Rarely, suxamethonium may cause malignant hyperthermia. Because it may cause fatal hyperkalemia, suxamethonium is contraindicated in patients with renal failure, neuromuscular disease, paraplegia and in those with muscular atrophy due to long-term ICU or hospital length of stay. In all such circumstances, avoidance of neuromuscular blockade or use of a rapid onset non-depolarising agent such as rocuronium is preferred.

**Hazards of using neuromuscular blockers**

These include:
- Life-threatening hypoxia in the event of accidental tracheal extubation. If the tracheal or tracheostomy tube becomes dislodged in a patient who has been paralysed the airway must be secured as rapidly as possible. If neuromuscular blockers have not been used there is usually some spontaneous respiratory effort that may be sufficient to delay the onset of life-threatening hypoxia.
- The aetiology of neuromuscular weakness complicating critical illness is multifactorial. Neuromuscular blockers are thought to be a contributory cause in some patients. Steroid-based neuromuscular blocking agents (pancuronium and vecuronium especially) are the most commonly implicated.
• Protective reflexes are also reduced. Measures to prevent corneal abrasion e.g. ‘eye tape’ should be instituted.
• Neuromuscular blockers exacerbate complications related to immobility. There is probably an increased risk of deep vein thrombosis, muscle wasting and peripheral nerve injury.
4. MEASURING AND MONITORING THE EFFECTS OF SEDATIVES, ANALGESICS AND NEUROMUSCULAR BLOCKERS

There is no easy way of doing this! No simple number for measuring the degree of soothing exists. This is not surprising when the various components of discomfort previously described are considered.

Level of analgesia

Accurate pain assessment is essential; it has been reported that 35% to 55% of nurses underestimate the patient’s pain. Patient self-report is the best guide to pain severity, specifically using a numeric pain rating scale ranging from 0 to 10. However, many critically ill patients are unable to communicate effectively because of cognitive impairment, sedation, paralysis, or mechanical ventilation. When patients cannot express themselves, observable indicators – both physiological and behavioural – have been used to evaluate pain in this population.

Pain assessment: communicative patients

The Numeric Pain Scale (NPS) employs a verbal rating of pain on a scale from 0 to 10, with 10 being the worst pain ever experienced, and is broadly used in a variety of clinical settings. Self-reported pain is considered to be the standard, and the NPS is recommended by SCCM (grade B recommendation).

Pain assessment: non-communicative patients

The COMFORT scale contains behavioural and physiologic factors (eight items, each scored from 1 to 5) to evaluate pain and was originally designed to assess distress in paediatric ICU patients. The scale measures alertness, calmness, facial tension, physical movement, muscle tone, ventilator respiratory response, blood pressure and heart rate, and exhibits good inter-rater reliability.

The Behavioural Pain Scale (BPS) is based on a sum score of three items: facial expression, movements of upper limbs, and compliance with mechanical ventilation. Based upon the assumption that a relationship exists between each score and pain intensity, each pain indicator is scored from 1 (no response) to 4 (full response), with a maximum score of 12. A limitation of BPS is that responsiveness (increase in score in response to noxious stimuli) decreases substantially with deepening levels of sedation. In addition, because compliance with mechanical ventilation may be considered to be a separate domain from the other behaviours, some intensivists only score facial expression and movements of upper limbs in order to assess the individual pain state.

A recently developed behaviour pain tool, the Critical Care Pain Observation Tool (CPOT), has four components: facial expression, body movements, muscle tension
and compliance with the ventilator for intubated patients or vocalisation for extubated patients. Each of these behaviours is assigned a rating of 0 to 2.

Current practice for adult ICU patients commonly includes a combination of NPS or a similar self-reported pain quantification tool plus an instrument designed to identify pain using behaviour and physiologic parameters in the non-communicative patient (e.g. the CPOT).


Level of sedation

Q. What are the various elements that constitute adequate comfort and sedation in the ventilated ICU patient?

A. The important elements are relief of pain and anxiety, hypnosis, respiratory depression to improve tolerance of mechanical ventilation and antitussive effects for tube tolerance.

It is important to remember that a mild irritating pain to one person may be a source of constant agony to another. Personality plays an important role in the perception of pain and discomfort. Nonetheless, drugs used to relieve pain and anxiety and promote sleep are all potentially dangerous and every effort should be made to monitor their effects. A variety of sedation scales have been described but one of the most commonly used is the Ramsay Scale (see figure below).

Other scales combine the sedation/arousal domain with an assessment of agitation, including the Sedation–Agitation Scale, which some authors recommend as an alternative, or the Richmond Agitation–Sedation Scale (RASS). See references below for further information and the full text pdf of the Jacobi reference.


Ramsay Scale for Assessment of Sedation

<table>
<thead>
<tr>
<th>Level/score</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anxious and agitated</td>
</tr>
<tr>
<td>II</td>
<td>Cooperative, oriented, tranquil</td>
</tr>
<tr>
<td>III</td>
<td>Responds only to verbal commands</td>
</tr>
<tr>
<td>IV</td>
<td>Asleep with brisk response to light stimulation</td>
</tr>
<tr>
<td>V</td>
<td>Asleep with sluggish response to stimulation</td>
</tr>
<tr>
<td>VI</td>
<td>Asleep without response to stimulation</td>
</tr>
</tbody>
</table>

It is important to appreciate that these scales are not ordinal scores. In other words moving from a score of 2 to one of 4 does not represent twice as heavy sedation.

Q. Sedation scores are relatively crude measures of the physiological effect of a drug, not least because they are discontinuous. What other variables could be used to titrate the dose of sedative and analgesic agents?

A. A number of physiological variables e.g. pupil size have been suggested as potentially useful for monitoring sedation/opiate effect. Heart rate and blood pressure may fall with excessive sedation and increase when sedation is inadequate. However, many other factors, especially a patient's underlying disease, intravascular volume status and drug treatment can influence heart rate and blood pressure. More sophisticated measures include changes in the R–R interval of the ECG and various derivations of the EEG. None is perfect and most are still being developed.

Haemodynamics

Unfortunately, many factors can influence such simple measurements as heart rate and arterial blood pressure. Although respiratory sinus arrhythmia (change in heart rate with respiration) has been used as a guide to depth of sedation, a variety of drugs and brain-stem disease can affect this variable.
**Neuromonitoring, including electroencephalograph**

Many different methodologies have been developed to process and simplify the electroencephalograph (EEG) signal. The goal is to quantify the EEG signal in a display that can be easily interpreted by clinicians. The Cooley and Tukey algorithm applied to the Fourier theorem – the Fast Fourier Transform – allows the EEG signal to be displayed as a spectral array. This concept has led to application of these monitors as tools for the objective measurement of the depth of sedation.

The Bispectral index (BIS) is composed of time domain, frequency domain, and high-order spectral sub-parameters. This integrates several disparate descriptors using a proprietary algorithm into a dimensionless index. The BIS displays a raw EEG trace obtained from a two-channel sensor but only from a unilateral prefrontal lobe site, and a power trend is displayed with a number from 0 to 100 (0 indicating no cortical activity and 100 indicating a patient who is wide awake). There are no units of measurement and one patient’s response to a sedative agent may be dependent on many factors, so whether a BIS number can correlate uniformly with depth of sedation remains uncertain. The effect of the electromyogram (EMG) signal may artificially increase the BIS number. A variety of other confounders, including sleep, drugs such as catecholamines, and temperature changes, may influence the BIS value.

The use of neuromonitoring as objective tools to assess depth of sedation in the ICU has not yet been universally embraced. The recommendations from the SCCM’s Clinical Practice Guidelines, published in 2002, do not endorse routine use of such devices. Although there is evidence for better operating room outcomes, such as early recognition of unintended awareness or better anaesthetic management, such evidence is very limited in the ICU setting. EEG is specifically useful to monitor the effect of sedation on epileptic status under continuous GABA-mimetic infusion as well as to avoid over dosage of barbiturate by checking the level of burst suppression. It may benefit some patients under deep sedation-paralysis or those with primary or secondary (e.g. septic encephalopathy) acute brain conditions who are at risk for sub-clinical electrographic seizures.


**Q. Why is the EEG difficult to use in the ICU?**

A. There may be interference from the many electronic devices in the ICU. The raw EEG is also difficult to interpret. Moreover, the resistance of the EEG electrodes may alter with the passage of time, further complicating interpretation.

Derivatives of the basic EEG, aimed at overcoming some of these difficulties, include those that present a graphical display of EEG frequencies, shown as a hill and valley display (spectral array). This method has shown some promise.
**Lower oesophageal tone**

The tone of the sphincter around the lower end of the oesophagus changes according to depth of sedation. A balloon can be placed in the oesophagus to measure the changes in sphincter pressure. This monitoring technique is rarely used in the critically ill.

**Effect of neuromuscular blockers**

Excessive muscle relaxation is unnecessary and potentially dangerous (see later). For example, prolonged overuse of muscle relaxants can be complicated by persistent residual weakness. A simple method of measurement is to discontinue administration of the agent until the patient is seen to move.

![Nerve Stimulator Image]

In most centres, monitoring the degree of neuromuscular block and adequacy of underlying sedation is performed using a combination of regular clinical and neurophysiological assessment. Long acting neuromuscular blockers are best monitored using a nerve stimulator. This technique, however, does not eliminate the risk of prolonged weakness.

Use of the nerve stimulator involves electrically stimulating a nerve containing motor fibres that supply a peripheral muscle, e.g. the facial nerve or the ulnar nerve. Twitching of the face or movement of the thumb are the respective responses. It is also possible to attach a strain gauge to the thumb allowing the movement to be measured or displayed on a screen. This can be useful during research. Unfortunately, it is difficult to maintain the strain gauge in the same position relative to the thumb and skin resistance changes often limit its value in the critically ill.

There are two ways electrical stimulation can be used:

- Four supra maximal stimuli are delivered (two per second). The last and first responses are compared. A 95% reduction in twitch height between the first and last response indicates surgical relaxation. This is shown below. This test can be repeated every 15 seconds or so.
Train of four stimulation to measure the effects of muscle relaxants

- An alternative is to look for the increase in a single twitch after tetanic stimulation. To do this test a single twitch is given followed by an electrical stimulus at 50Hz. A further single twitch is given and if the effects of neuromuscular blockers are still present the second twitch will be greater. This approach is illustrated below. This test can only be performed every 30 minutes, because the neuromuscular junction needs to recover.

Post-tetanic facilitation after neuromuscular blockers
5. MANAGING ADVERSE EFFECTS AND COST/BENEFIT ISSUES OF SEDATIVE DRUGS

No drug is completely safe. Sedatives in particular have serious side effects. Both under-sedation and over-sedation are dangerous. The balance between the two is shown below.

Over-sedation is probably more common than under-sedation. This is because under-sedation is easier to recognise and the patient's attendants do not like to see a patient in distress. The effects of over-sedation are more insidious and difficult to recognise but just as dangerous.

In the figure above a variety of adverse effects are described. Read the list and see if you can work out the mechanisms.

Link to ESICM Flash Conference: Sonja Fruhwald, ‘How to avoid GI side-effects (of opiates)’ ESICM congress, Vienna 2009

Metabolites

Drugs are metabolised, usually from fat soluble compounds (hence able to cross membranes and be active) to being water soluble (hence inactive and able to be excreted in bile and urine). Some metabolites, however, are active and potentially dangerous. Some common examples are shown in the table below.
<table>
<thead>
<tr>
<th>Parent drug</th>
<th>Metabolite</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Nor desmethyl diazepam</td>
<td>Both metabolites are active and have a longer duration of action than the parent drug.</td>
</tr>
<tr>
<td></td>
<td>Oxazepam</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>1-hydroxymidazolam</td>
<td>Both are active, although much less so than the parent drug. The glucuronide may be retained in renal failure</td>
</tr>
<tr>
<td></td>
<td>1-hydroxy midazolam - glucuronide</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine-3-glucuronide</td>
<td>Both are active. M-3-G is probably antianalgesic.</td>
</tr>
<tr>
<td></td>
<td>Morphine-6-glucuronide</td>
<td>M-6-G is more active than the parent as an analgesic.</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Norpethidine</td>
<td>Metabolite may cause seizures</td>
</tr>
<tr>
<td>(Meperidine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Nor desacetyl vecuronium</td>
<td>The metabolite may be a cause of prolonged paralysis</td>
</tr>
</tbody>
</table>

**Solvents**

Because they are fat soluble most drugs are dissolved in an organic solvent, many of which are potentially toxic. Because sedative and analgesic agents are often given as a prolonged, continuous, intravenous infusion, the solvent may accumulate and cause toxicity.

Propofol is solubilised in soya bean extract – which is a fat. If large amounts of propofol are given the solvent can accumulate and is a potential cause for toxicity. New formulations using 2% propofol may be preferred to the older 1% preparations in an attempt to minimise fat administration.

In adult ICU patients, propofol infusion syndrome (PRIS) is a rare (about 1%
incidence) but potentially lethal complication, especially if there is no early identification of the syndrome. The physiopathology is not entirely clear, however a dysfunction of the mitochondrial respiratory chain seems to be involved and genetic factors may contribute. Clinical features consist of arrhythmias, hyperlactatemia with metabolic acidosis, hyperlipemia, rhabdomyolysis, myoglobinuria. PRIS has been described classically in children and young adults undergoing a long-term infusion with propofol (more than 48 hours) at doses higher than 4 mg/kg per hour. However, it can be observed with lower doses and in shorter duration sedation. Steroids, vasopressors and low carbohydrate intake are predisposing factors.

In many countries, using propofol to sedate children is no longer approved.


The elimination of drugs may vary in the presence of critical illness because of disturbance of enzyme function and inadequate excretion. Solvents may also be similarly affected.

**Anecdote**

A 46-year-old female, former ICU patient, complained to one of the ICU consultants that she had not been well treated while a patient in the ICU. Careful listening to her complaint and examination of the notes revealed the explanation. During her stay she had needed a rectal examination and a high vaginal swab. On both occasions she had been receiving midazolam and propofol, both of which can cause hallucinations. Midazolam is particularly well recognised as causing misinterpretation of physical stimuli resulting in sexual hallucinations.

Q. In light of the foregoing story how might the information affect your clinical practice?

A. Additional caution when performing sensitive procedures including careful explanation of the purpose of the procedure and chaperoning wherever possible.

**Drug interactions**

Midazolam is metabolised by the enzyme cytochrome, P450 3A4. This enzyme also metabolises many other drugs commonly used in the critically ill. Substances that are metabolised by this enzyme may either inhibit or enhance its activity. Erythromycin, a macrolide antibiotic commonly used for community-acquired e.g. atypical pneumonia, is a potent inhibitor of cytochrome, P450 3A4.

**Anecdote**

A 65-year-old man was admitted to hospital with a community-acquired pneumonia for which he was given erythromycin and cefotaxime. His clinical condition deteriorated and he needed mechanical ventilation. For comfort an infusion of midazolam (with morphine) was started. Six days later the midazolam was stopped. He remained comatose for four days later. A CT scan of his brain and a lumbar puncture were both normal. Flumazenil (a benzodiazepine antagonist) was given and he awoke immediately. In this patient midazolam was associated with unexpectedly prolonged coma, probably because erythromycin had inhibited cytochrome P450. As a result unnecessary tests were performed causing undue concern to the patient’s relatives.

Q. What simple manoeuvre might you have carried out to avoid this complication?

A. ‘Daily wakening’. Alternatively the midazolam could have been changed to a more predictable agent such as propofol a few days before sedation was likely to be discontinued. Flumazenil could have been given diagnostically before deciding to perform a CT.

**Unexpected effects**

Many drugs have effects on organs other than those at which they were primarily targeted. Morphine, for example, is a powerful analgesic that has effects not just on the μ-receptor but also on endocrine function, drug metabolism, renal function and the immune system. In the event of new unexplained signs or symptoms it is always worth considering sedative and analgesic drugs as a possible cause.

A notable example of such an event occurred with etomidate, an intravenous anaesthetic induction agent which was subsequently used as a sedative agent in the critically ill in some countries. The agent proved to be a potent inhibitor of the cytochromes P450 that are responsible for the manufacture of cortisol. As a consequence some patients developed a fatal Addisonian crisis.
Anti-depressants

Although there is no good evidence to support the use of these drugs in the critically ill they are commonly prescribed. Many seriously ill patients develop an appropriate reactive depression that does not respond well to conventional anti-depressants. Furthermore, anti-depressants take many days to work and they are not without side effects.

An 82-year-old man who developed a community-acquired pneumonia, was admitted to the intensive care unit and spent three weeks on a ventilator. He was awake with no sedation because he had a tracheostomy. Understandably he became depressed. Nursing staff raised the question of starting him on an anti-depressant but it was decided that drug therapy was not indicated. Ten days later as his condition improved, he started mobilising and had a daily plan of activities. He was no longer depressed (without drug therapy) and felt relaxed and was looking forward to his discharge from the intensive care unit.

Neuromuscular blockers

The use of neuromuscular blockers (NMBs) is not without risk – most obviously the inability to breathe spontaneously if disconnected from the ventilator. NMBs may also predispose to the development of critical illness weakness. The incidence of complications may be reduced if the use of NMBs is restricted and their administration carefully monitored.

Neuromuscular weakness in the critically ill has many causes some of which are listed below. Pathological studies have demonstrated features of axonal degeneration and myopathy.

Some of the factors contributing to neuromuscular weakness:
- Critical illness polyneuropathy and its associated factors. Link to PACT module on Neuromuscular conditions
- Residual effects of neuromuscular blockers or their metabolites
- Concomitant disease
- Poor nutrition
- Duration and severity of illness and treatment
- Drugs
  - muscle relaxants (neuromuscular blockers)
  - corticosteroids
  - antibiotics
**Effects of age and disease**

The extremes of age alter sedative requirements. The very old usually need less of a particular drug, whereas children generally need more. This variation in dose requirements represents changes in both metabolic ability and receptor sensitivity. Other mechanisms include changes in total body water that may alter the volume of drug distribution.

Think about how small children need large doses of drugs (in terms of mg/kg) while frail elderly people need much less and have a greater propensity to develop cardiovascular instability.

**Modifying approach in response to cost/benefit issues**

Sedative drugs contribute significantly to the overall drug budget of an intensive care unit. This is because they are often used continuously for many days or even weeks in some patients. Although propofol is considered as an anaesthesia induction agent (for use in the operating rooms), in some hospitals, up to 60% of the overall hospital use of this agent, is in the intensive care units. Implementation of protocols for target sedation and daily interrupted sedation may reduce costs.

Link to PACT modules on Quality assurance and cost-effectiveness and Organisation and management

Select a group of ten patients in your ICU. Try to choose a variety of both patients (including long-stay) and sedation techniques. Detail the specific agents used and their total dosage. Then ask your pharmacy colleagues to help cost the medication. Notice older agents are less expensive than newer drugs.

**Note** It is important also to remember that the acquisition cost of drugs is not the only crucial factor. Cheap drugs may work out as the most expensive if they are associated with serious adverse effects or if they prolong the awakening of the patient. Synergistic combinations of drugs and careful thought about the most appropriate agent for an individual patient will lead to a reduction in wastage.
Ask the ICU manager how much a day in the ICU costs. Compare it to the prices in the previous activity. The cost of one day in the ICU is usually many times the cost difference between an older and newer agent. If newer agents are more reliable then the overall cost savings derived from their use can be significant.

Not all costs are financial. For example, tracheostomies which may be required in heavily sedated patients, to facilitate long-term mechanical ventilation, have been recommended for long-term weaning. Although percutaneous tracheostomy has made this easier and scars are less visible, it would be an unacceptable consequence of excessive sedation if this were the reason for which the tracheostomies were required.

Remember tracheostomy is associated with significant risks, even if these are less than those of prolonged tracheal intubation. Even the scarring of the neck may be a subsequent social problem, especially in young women, when it may commit them to a lifetime of polo-neck sweaters.

**Anecdote**

A 17-year-old female was treated for meningococcal sepsis. At 14 days a tracheostomy was considered to help weaning, since she became agitated about her oro-tracheal tube each time the sedation was stopped. Because of concerns about scars a naso-tracheal tube was used (although this does carry the risk of infection in the para-nasal sinuses). This patient was weaned successfully over the next four days.

Link to PACT module on Airway management (Tracheostomy)
CONCLUSION

In this module we considered the two main categories of drugs – sedatives and analgesics and noted their overlapping and adverse effects. The importance of the individual needs of patients was developed in Task 2 where methods for giving drugs by intravenous and other routes of administration, such as epidural infusion, were a focus and drug interactions were covered. Monitoring the effects of drugs e.g. by sedation scales or train of four stimulation (for neuromuscular blockade) is necessary because of their potential hazards. There is a need to strike a balance between under- and over-sedation and drug interactions. It is important to be aware that unexpected effects can result from factors such as the age of the patient. Financial and non-financial costs associated with sedation in ICUs were raised.
SELF-ASSESSMENT QUESTIONS

EDIC-style Type K

1. Which of the following drugs usually cause amnesia?
   A. Benzodiazepines
   B. Propofol
   C. Ketamine
   D. α-2 agonists

2. Characteristics common to all benzodiazepines
   A. They relieve anxiety
   B. They are antipsychotic
   C. They are a cause of amnesia
   D. They are a cause of respiratory depression

3. When midazolam is used as a continuous infusion, consider the following statements
   A. May cause prolonged effects due to the active metabolite 4-hydroxymidazolam
   B. Prolongs sedation in acute renal failure
   C. Leads to haemodynamic instability
   D. In alcoholic patients, the anticipated drug effect usually requires a higher dosing regimen

4. Regarding the use of propofol as sedation in the ICU
   A. Is best given in intermittent rather than continuous doses
   B. Is well tolerated regarding cardiovascular stability
   C. Usual maintenance dose is 10 mg/kg/h
   D. The use of concentrated solution 20 mg/ml is advocated to reduce the dose of fat administered

5. Ketamine
   A. Inhibits arterial catecholamine actions
   B. Stimulates the GABA A receptors
   C. Has bronchodilator properties
   D. May produce nightmares

6. Concerning the use of neuroleptics in the ICU
   A. Should always be added to ordinary sedation regimen to prevent delirium
   B. Is the drug group of choice in the treatment of ICU delirium
   C. Is a cause of the so-called delta wave in the ECG
   D. Carries little risk of respiratory depression

7. Regarding morphine in the critically ill patients
   A. Is usually given in doses from 0.1 to 0.5 mg/kg/h
   B. Causes accumulation in renal failure
   C. The metabolite morphine-6-glucuronide (M-6-G) is in itself a potent analgesic
   D. The metabolite morphine-3-glucuronide (M-3-G) is in itself a potent analgesic
8. NSAIDs are not often used in the ICU patients because of
   A. Risk of gastrointestinal bleeding
   B. Platelet inhibition
   C. Risk of generalised vasospasm
   D. Risk of renal failure

9. Daily interruption of sedation in the ICU may
   A. Cause less amnesia and lead to increased problems in ICU survivors
   B. Increases the use of analgesics required
   C. Shortens the ICU length of stay
   D. Result in a reduction in the duration of mechanical ventilation

EDIC-style Type A

10. Regarding the use of neuromuscular blocking drugs in the ICU, which one of the following statements is TRUE?
   A. Is usually required to perform mechanical ventilation
   B. Can be used to facilitate the use of non-invasive ventilation
   C. Should not be used without proper sedation and analgesia
   D. Is required to facilitate endotracheal intubation
   E. Should not be given in patients with renal failure

11. Which one of the following sedation drugs is least prone to accumulation?
   A. Diazepam
   B. Midazolam
   C. Thiopentone
   D. Propofol
   E. Haloperidol

12. After a prolonged sedation with midazolam (7 days), an ICU patient is allowed to wake up. What is the most appropriate action to take regarding the further use of sedation in his patient?
   A. Gradually decrease the dose to zero during the next 2–3 days
   B. Stop infusion of midazolam immediately
   C. Stop infusion of midazolam and continue 2–3 days with propofol
   D. Stop midazolam infusion and add low dose morphine
   E. Stop infusion of midazolam and give flumazenil if the patient is still sedated the next day

13. Which statement about the use of alpha-2-agonists in the critically ill is true?
   A. Acts through stimulation of the N-methyl-D-aspartate (NMDA) receptors
   B. Clonidine is a pure alpha-2-agonist
   C. Dexmedetomidine is about twice as potent as clonidine
   D. Seldom cause respiratory depression
   E. Have no significant analgesic effects
14. Opioids are often divided into naturally occurring (opiates) and synthetic agents; which of the following opioids is NOT synthetic?
   A. Pethidine
   B. Codeine
   C. Fentanyl
   D. Alfentanil
   E. Phenophendine

15. Which of the following drugs should NOT be given as an epidural infusion?
   A. Morphine
   B. Fentanyl
   C. Clonidine
   D. Bupivacaine
   E. Midazolam

16. Regarding the use of the synthetic opioids, fentanyl, alfentanil and sufentanil in critically ill ICU patients, which of the statements is FALSE
   A. They may all accumulate after continuous infusion
   B. Sufentanil is the most potent of the three
   C. Alfentanil is usually given in doses of 0.5–2 mg/kg/h
   D. Fentanyl is 10 times more potent than morphine
   E. Fentanyl does not release histamine
Self-assessment Answers

1.  
   A. T  
   B. F  
   C. F  
   D. T  

2.  
   A. T  
   B. F  
   C. T  
   D. T  

3.  
   A. F  
   B. T  
   C. F  
   D. T  

4.  
   A. F  
   B. F  
   C. F  
   D. T  

5.  
   A. F  
   B. F  
   C. T  
   D. T  

6.  
   A. F  
   B. T  
   C. F  
   D. T  

7.  
   A. F  
   B. T  
   C. T  
   D. F  

8.  
   A. T  
   B. T  
   C. F  
   D. T  

9.  
   A. F  
   B. F  
   C. T  
   D. T  

10.  Answer C is correct  

11. Answer D is correct  

12. Answer B is correct  

13. Answer D is correct  

14. Answer B is correct  

15. Answer E is correct  

16. Answer D is correct
PATIENT CHALLENGES

A 57-year-old female patient is readmitted to your hospital. Six weeks earlier she had been diagnosed as suffering from Wegener’s granulomatosis – a condition characterised by necrotising granulomatous vasculitis which can affect the lungs and kidneys. She responded well to treatment with a monoclonal antibody and corticosteroids. On this occasion the patient is febrile and has a productive cough but her major complaint is of pain in her mouth from ulcers. The pain appears to be responsive only to morphine. Her physicians suspect that her vasculitis has recurred. Two days later she is admitted electively to your intensive care unit (ICU) for treatment with a different monoclonal antibody. The admission is thought necessary in case the treatment is associated with serious adverse effect – in the event, a wise precaution.

Two days after admission she bleeds into her lungs, deteriorates with respiratory distress and hypoxaemia and mechanical ventilation is indicated. The patient, however, simply wants morphine in sufficient amounts to relieve the pain from her mouth ulcers. If the treatment causes respiratory depression and her death as a consequence, this is her wish.

A long discussion with the patient and her family ensues. Finally, there is agreement to start ventilation and do whatever else is necessary for 48 hours so long as the patient is pain free and adequately sedated.

Links to other modules
PACT module on Mechanical ventilation
PACT Module on Communication skills
PACT module on Ethics (Patient Autonomy)


Sedation requirements for maintenance of mechanical ventilation
Communication with patients, relatives and professional colleagues
Appropriate documentation of events

Q. Having obtained patient consent how would you provide sedation/induce anaesthesia for this patient to facilitate elective intubation and mechanical ventilation? Prompt: The patient is fully conscious and haemodynamically stable.

A. In this patient, the use of a rapid sequence induction and neuromuscular blockade for tracheal intubation is reasonable and safe in experienced hands.
Q. What drugs would you use to meet this patient’s request that she be kept asleep while being ventilated for 48 hours? Explain your answer.

**Prompt: As agreed with the patient you plan to stop mechanical ventilation within 48 hours.**

A. Your preference is for a combination of drugs to maintain good quality pain relief and a moderate level of sedation. After tracheal intubation, pain is controlled by the intermittent administration of morphine, and midazolam and propofol are tried individually for sedation. Neither is satisfactory. Sedation is eventually maintained with a combination of midazolam and propofol – both given by continuous infusion. Morphine is given by IV bolus as required. The combination gives greater haemodynamic stability than the use of either agent alone and is expected to allow relatively prompt awakening.

At the end of the 48 hours the situation is worse. To maintain a PaO$_2$ of 60 mmHg (8 kPa), an inspired oxygen concentration (FiO$_2$) of 0.95 with reversed ratio ventilation and 10 cm H$_2$O positive end-expiratory pressure (PEEP) are needed. Chest X-ray confirms the presence of intrapulmonary haemorrhage. Renal function is deteriorating, with a plasma creatinine twice the upper limit of normal. Gut function has also deteriorated such that total parenteral nutrition is now needed. Hypotension associated with oliguria and a rising lactate prompts the use of inotropes.

Q. Oxygenation is poor and you opt to utilise neuromuscular blockade at least initially to achieve an optimal ventilatory pattern. What would be your choice and how would you measure its effects?

A. In addition to the analgesia/sedation, intermittent intravenous injection of atracurium is an appropriate choice, its effects being measured by train of four monitoring to avoid overdosing.

**Learning Issues**

- Indications for the use of neuromuscular blockers
- Monitoring of neuromuscular blockers
- Choice of appropriate sedative and analgesic drugs either alone or in combination
Q. Your patient's condition is clearly deteriorating. There is now evidence of renal, gut and cardiovascular dysfunction. Some modification of the sedation regimen will be required as additional treatments are brought into play. How would you plan subsequent management?

Prompt: Renal failure may cause accumulation of some of the sedative drugs you are using. Both morphine and midazolam have active metabolites. Pancuronium is eliminated more slowly in renal failure.

A. You are aware that the deterioration in renal and cardiovascular function may mean that the effects of sedation will be more profound and protracted. You therefore decide to alter the sedation programme in light of the planned changes in treatment.

Learning Issues
Effect of renal dysfunction on sedation requirements
Effect of sedative/analgesic drugs on gut and cardiovascular function

The original agreement was that if the patient was not better at 48h treatment would stop. At this time, however, the admitting physicians suggest that plasmapheresis be tried. After lengthy discussion involving the patient’s relatives and seeking advice from colleagues, implementation of this treatment is agreed. You stop the combined sedation and use midazolam alone by infusion, still with intermittent morphine and now, pancuronium (for longer duration of neuromuscular blockade).

The oliguria did not improve, acute renal failure supervenes and the next day, continuous veno-venous haemodiafiltration (CVVHD) is started. Both the morphine and the pancuronium had been given by intermittent injection when needed, making accumulation less likely.

Links to other modules
PACT module on Oliguria and anuria
PACT module on Acute renal failure

On several occasions over the next few days you stop the midazolam (Table below) and restart when the patient has regained consciousness. The first time you stop midazolam it took 10 hours for the patient to wake. Thereafter, you start at half this dose.

Learning Issues
Daily interruption of sedation
Advantages/disadvantages of combinations of sedative agents
Options for routes of administration
'Recovery times' for various sedative agents
Time to regaining consciousness on stopping midazolam

<table>
<thead>
<tr>
<th>Days after ventilation</th>
<th>FiO₂</th>
<th>Midazolam infusion (mg/h)</th>
<th>Time to regain consciousness (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.95</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.55</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>last CVVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.55</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>0.35</td>
<td>2-3</td>
<td>roused by voice</td>
</tr>
<tr>
<td>18</td>
<td>off ventilator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0.35</td>
<td>stop</td>
<td></td>
</tr>
</tbody>
</table>

**Q.** During the periods when you wish to maintain a stable level of sedation in this patient how might you assess sedation requirement?

A. There are many sedation scores in use. What is important is not which score is chosen but that it is used regularly and intelligently.

**Note** Also remember that these are not really scores (which implies an ordinal relationship between the numbers) but scales. What this means is that moving from a sedation score of 2 to 4 does not mean sedation is twice as deep, merely that sedation is deeper.

**Learning Issues**

*Sedation scales*

**Q.** What is the ideal level of sedation?

A. The ideal level of sedation varies from patient to patient, with severity of illness and with the passage of time. Some patients may require moderately deep sedation while others may be comfortably wide awake, watching television but needing 70% oxygen with reversed ratio ventilation on high levels of PEEP.

**Note** Determining the 'ideal' level of sedation in an individual patient is currently a largely subjective task. Analgesia is key.

Time has moved on and your patient has now been critically ill for more than two weeks and throughout this period has had her plasmapheresis and has been receiving a variety
of treatments for multi-organ dysfunction. Ultimately, she shows signs of a steady recovery and you begin to make plans for disconnecting her from the ventilator, extubation and ultimately for her return to the ward.

**Q.** Is there a routine for withdrawing sedation from critically ill patients?  
*Prompt: Generally speaking, the sicker the patient has been and the longer the period of care, the more protracted the weaning process will be.*

A. Just as weaning from ventilation needs to be matched to the patient, so does sedation. For some patients abrupt cessation of all sedation is entirely effective and safe. Others (like this lady) need a slower withdrawal process.

On the 25th day after admission to the ICU the patient is discharged to the ward. She is grateful that you continued to treat her. She does not remember the earlier conversations. She is weak and this is felt to be caused by her Wegener's granulomatosis, probably with a contribution from her critical illness associated weakness, to which she was predisposed by the administration of corticosteroids and pancuronium.

**Q.** The ward staff are naturally anxious to ensure that the patient continues to improve but have little experience of such cases. What action would you take to deal with this?  
*Prompt: Effective communication with patients/relatives/colleagues is all important.*

A. The ICU staff should consider taking opportunities to visit the patient and ward staff after discharge from the ICU to review patient progress and share their experience and expertise. Some units have more formalised follow-up rounds that may also incorporate care of practical matters such as drug withdrawal, post ICU dreams/dysphoria and tracheostomy management/decannulation.

**Learning Issues**

Neuro-psychiatric sequelae of sedation/critical illness

**Q.** In the event that this patient was in fact being discharged to another hospital how would this modify your approach to management?

A. Substitute written information and telephone discussion.

**On reflection.** Appropriate sedation and analgesia is central to facilitating the provision of successful critical care to the patient. Sedation/analgesia regimens are part of overall critical care management but require individualisation to patient need. Physical/common sense options for patient comfort, including polite explanation/communication, are key. The choice of individual drugs where necessary, and their optimum mode of administration, is outlined. Daily interruption of sedation protocols may be important in guarding against over-sedation; recognition of the time to stop and mode of stopping sedation is important to minimising the duration of ICU stay. Dealing with drug withdrawal states is an occasional need. Follow up of patients is illuminating as many, particularly the longer stay patients, have unpleasant dreams or other neuro-psychiatric sequelae which appear to have a relationship with the character of the sedation and the memory of ICU.