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The Use of Sedative Agents in Critically Ill Patients

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Summary

The main aim of sedation in the critically ill patient is to provide relief from anxiety and pain. The current, ideal level of sedation should leave a patient who is lightly asleep but easily roused. No single regimen is suitable for all patients. The level of sedation should be monitored, and the choice of agent, the dose and the route of administration adjusted appropriately.

Midazolam is often used to provide sleep and anxiolysis. Alternatives include propofol and isoflurane. Propofol is easily titrated to achieve the desired level of sedation, and its effects rapidly end when the infusion is stopped. Isoflurane also appears promising, but special equipment is needed for its administration. Morphine is the standard analgesic agent. The principal metabolites, morphine-6-glucuronide, is also a potent opioid agonist and may accumulate in renal failure. Of the newer analgesic agents, alfentanil is an ideal agent for infusion, and may be the agent of

choice in renal failure. Neuromuscular blocking agents are indicated only in specific circumstances, and used only once it is known patients are asleep and pain free.

The actions of these agents are unpredictable in the critically ill patient. Alterations in drug effect and elimination may occur, especially in the patient with hepatic and renal failure. This may also apply to active metabolites of the parent drug.

When planning sedation regimens, specific patient needs and staffing levels must be remembered. Attention to the environment is also important. Midazolam and morphine given by intermittent bolus or by infusion are the mainstay of most regimens. Propofol is ideal for short periods of care on the ICU, and during weaning when longer acting agents are being eliminated.

1. Aims of Sedation

Sedation has been described as the process of soothing. The principal aims of sedation in the critically ill are to provide analgesia and anxiolysis. In some patients amnesia, respiratory depression and an antitussive effect may also be desirable. Different goals are needed in each patient and their individual requirements change as their disease process improves or worsens.

There is no single universal depth of sedation or single sedative regimen suitable for all patients (fig. 1). The regimen used will depend on the sickness of the patient and how long they are expected to stay in the intensive care unit. There is a general tendency towards oversedation, partly to ensure patient comfort, but also because it may be easier to care for a critically ill patient who is unresponsive. Although the risks of undersedation are widely recognised those of oversedation are less well known (table I). The total abolition of pain may not be desirable, since an active stress response is beneficial and patients are comfortable if their pain is controlled rather than absent (Manara et al. 1990). The level of sedation thought to be ideal has changed in the last decade. In 1981 Merriman showed that 67% of intensive care units aimed to have their patients completely detached from their environment. In a subsequent survey, Bion and Ledingham (1987) found that the perceived ideal level of sedation had changed, most intensive care units now aiming for a patient who was sleepy but easily roused. Deep sedation, with the patient virtually anaesthetised, is now reserved for a few specific indications. These include patients with tetanus (where it may be used to suppress the autonomic effects), those with critical oxygenation (in whom a reduction of oxygen consumption may be desirable) and patients with severe head injuries (where it is necessary to reduce cerebral oxygen consumption and to prevent coughing and straining which will increase intracranial pressure).

In some patients adequate sedation can be achieved by close attention to the environment. The

Table I. The risks of under- and oversedation

Risks of undersedation	Risks of oversedation
Discomfort	Coma
Pain	Respiratory depression
Hypertension	Hypotension
Tachycardia	Bradycardia
Failure of the ventilator to synchronise with the patient (causing hypoxia and hypercapnia)	Ileus
	Renal failure[a]
	Venous stasis
	Immunosuppression[b]

a Hill et al. (1991).
b Tubaro et al. (1983); Moudgil (1981).

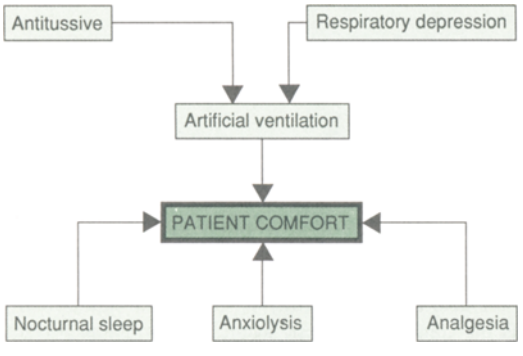

Fig. 1. The aims of sedation.

provision of a television or radio and sympathetic and kind words from the staff may be all that is needed. The ideal level of sedation will also vary between intensive care units. Staffing levels, particularly levels of nursing staff, will alter the way drugs are administered. Units that are well staffed tend to have their patients more lightly sedated and use intermittent administration of sedative and analgesic drugs titrated with precision to the patient needs. Nurses in these units can also spend more time reassuring the patients and generally attending to their comfort. A greater number of medical staff will allow more time for techniques such as regional analgesia. In addition, the type of equipment available will also alter sedative requirements. The introduction of sophisticated ventilators (Sladen & Jenkins 1978) and air or bead beds has led to a reduction in sedative requirements.

Some patients will prove impossible to sedate using conventional techniques. In these patients other agents should be tried until satisfactory sedation is achieved.

2. *Monitoring Sedation*

Sedative drugs are not innocuous and may contribute to continued morbidity and possibly mortality in the critically ill. To overcome some of the problems of unnecessary oversedation, sedation scoring should be routine in all patients. Scoring of sedation is analogous to the recording of haemodynamic changes after inotropes, indices of infection after antibiotics and blood glucose after the administration of insulin. It is difficult to monitor sedation using physiological end-points as there are no devices which monitor patient comfort and give a numerical readout. In addition, monitoring scales are subjective and depend upon observation of the patient. This task, in common with other monitoring functions, is usually delegated to the nurse at the bedside. A variety of sedation scores have been developed over the years and a simple, effective and reproducible scale (fig. 2) is the one used in the Addenbrooke's Intensive Care Unit (O'Sullivan & Park 1990). This is recorded each hour. The first level is 'agitated' when the patient may show distress, pain or anxiety and represents inadequate sedation. The second level, 'awake', indicates an alert patient who is not distressed. The third level is lightly asleep but easily roused by voice. These last 2 levels are currently thought to represent an ideal level of sedation. The fourth and fifth levels of 'roused by tracheal suction' and 'unrousable' represent a level of sedation that is now considered excessive. This last level is equivalent to deep coma of whatever cause. The score for paralysis means that sedation has not been assessed due to the effect of the neuromuscular blocking drugs. It aims to highlight the fact that concomitant sedation may be appropriate. The final level, 'asleep', is often the most valuable. During sleep, sedation is not assessed and this line is meant to represent a patient who is thought to be asleep but would wake up in the normal way to soft verbal or light physical stimuli. Using this system it is possible to find out how much sleep the patients have had in the previous 24 hours, so that any patient who becomes sleep deprived can be treated. Future versions of the scale will have 2 further lines to allow assessment of pain relief and tolerance to ventilation.

Agitated					
Awake					
Roused by voice					
Roused by tracheal suction					
Unrousable					
Paralysed					
Asleep					

Fig. 2. Addenbrooke's Hospital Intensive Care Unit Sedation Scale.

Nocturnal sedation is thought to be desirable in the critically ill, although scientific evidence to support this is lacking. Patients in the intensive care unit after major noncardiac surgery have been found to be severely sleep-deprived (Aurell & Elmqvist 1985). Kornfeld and colleagues (1965) and Lazarus and Hagens (1968) have stressed the importance of sleep after open heart surgery. As the duration of care on the ICU is usually short in this

group of patients the effects of sleep deprivation are probably self-limiting. However, in other patients who require intensive care for longer periods, sleep deprivation may be an important contributory cause of the psychosis seen in these patients. Sleep deprivation leads to loss of body nitrogen (protein synthesis and cell division being greater during sleep) and evidence indicates that hypnotics may help the restoration of tissues by promoting sleep (Adam & Oswald 1984). Despite the lack of information, many intensive care units do use night sedation and anecdotally patients do feel better after a 'good night's sleep'.

3. Drugs Used for Sedation and Analgesia

3.1 Drugs That are Principally Hypnotic

3.1.1 Benzodiazepines

This is the most common group of drugs currently used to provide hypnosis and anxiolysis. Many of this group will also induce amnesia. Diazepam, the first drug in this group to be used, has an active metabolite, demethyl-diazepam, which has a longer elimination half-life than the parent drug itself (Mandelli et al. 1978). The pharmacokinetics are not affected by renal impairment but there is reduced clearance in liver disease (Bellantuono et al. 1980).

Lorazepam has been used by intermittent intravenous injection to provide sedation for critically ill patients (Dundee et al. 1976). However, its use has not been widely accepted because of its long duration of action and accumulation.

More recently midazolam has been used (Shelly et al. 1991). It has a shorter duration of action than diazepam and is presented as a water-soluble salt, making it easier to give peripherally. The principle metabolite is α-hydroxy-midazolam, which is less active than midazolam (10%). Midazolam is stored in a solution with a pH of 4 and at physiological pH the ring structure of the molecule changes, making it lipophilic and conferring the sedative action. In some patients midazolam may not provide adequate sedation despite large doses by infusion. This may represent a point where a further increase in the midazolam dose is beyond the maximal enhancement of the GABA-ergic inhibitory system and so has no clinical effect. Although prolonged action (due to changes in the metabolism of midazolam) has been reported (Shelly et al. 1987), it is the most predictable of all the benzodiazepines.

The advent of the benzodiazepine antagonist, flumazenil, has decreased the problems of excessive sedation due to this group of drugs (Bodenham et al. 1988; Brogden & Goa 1988). The development of a specific antagonist should not, however, be seen as an excuse for iatrogenic agonist overdose (Park & Gray 1989). Caution is necessary with this antagonist in patients with raised intracranial pressure, when rapid reversal of sedation may further increase intracranial pressure (Chiolero et al. 1988).

3.1.2 Propofol

This agent is achieving widespread popularity for sedation. It was initially introduced as an intravenous induction agent for anaesthesia. It is short-acting and usually needs to be given by continuous intravenous infusion (Aitkenhead et al. 1989; Langley & Heel 1988). Unwanted effects include arrhythmias, hypotension, fat overload and occasionally green urine and hair. Owing to its formulation in soya bean extract it may enhance oxidative drug metabolism in some patients (Burgess et al. 1987). It is expensive, but at present is the most predictable hypnotic. Even after several days of use its effects are rapidly terminated when the infusion is discontinued.

3.1.3 Clomethiazole (chlormethiazole)

Clomethiazole is a vitamin B derivative. Its use in the critically ill has been described (Scott et al. 1980) although continued use may lead to accumulation and careful dose titration is essential (Gray & Park 1989). Excessive fluid administration can be a problem except in patients with renal failure receiving more sophisticated methods of renal support. Clomethiazole may exert a protective effect against septic shock in animal models (Modig 1988).

3.1.4 Anaesthetic Agents

Nitrous oxide was described over 30 years ago for sedation in patients with tetanus (Lassen et al. 1954). The subsequent recognition of bone marrow depression has limited its use (Lassen et al. 1956). More recently isoflurane, a short-acting volatile anaesthetic agent with minimal metabolism, has been studied (Kong et al. 1989). This approach appears promising but concern over cost and possible renal toxicity from fluoride has been raised (Park & Burns 1989). In healthy patients receiving isoflurane for surgical anaesthesia the metabolism of fluoride is of insufficient magnitude to cause renal dysfunction (Mazze et al. 1974). However, in critically ill patients prolonged administration of isoflurane may result in potentially nephrotoxic serum concentrations of fluoride (Truog & Rice 1989). Furthermore, nephrotoxicity may depend not only on the peak plasma concentration but also on such factors as the preexisting renal condition, coadministration of nephrotoxic drugs, duration of exposure and the underlying disease process.

3.2 Drugs that are Principally Analgesic

3.2.1 Morphine and its Derivatives

This group of drugs comprises morphine, papaveretum, codeine and diamorphine (diacetylmorphine). Morphine is a standard drug used throughout the world. A comparison between the pharmacokinetics of morphine with other opioids is shown in table II. The principle site of morphine metabolism is the liver (Bodenham et al. 1989). It is metabolised mainly to water-soluble compounds, which include morphine-6-glucuronide, morphine-3-glucuronide and normorphine.

Morphine-6-glucuronide (M6G) is highly active (Shimomura et al. 1971). When given subcutaneously to mice it is 4 times more active and approximately 2 times as long in duration as morphine given by the same route, and given intracerebrally M6G is approximately 40 times more active than morphine.

Therefore, in renal failure M6G will accumulate and prolonged narcosis has been reported (Osborne et al. 1986; Shelly et al. 1987). M6G has been thought to be highly polar and therefore unable to penetrate the blood-brain barrier, but recent work has shown that it may be able to change its configuration according to its environment (Carrupt et al. 1991).

Diamorphine and papaveretum appear to have no significant advantages over morphine for use in critically ill patients. However papaveretum is still widely used in the United Kingdom and Australasia. It is a mixture of alkaloids, consisting of morphine, codeine, noscapine, papaverine and narcotine. The pharmacology of some of these alkaloids and their interactions with other drugs is not known. In addition, concern has arisen that noscapine may be genotoxic (Gatehouse et al. 1991) and the Committee on Safety of Medicines (1991) has now advised that all products containing papaveretum should be contraindicated in women of

Table II. Pharmacokinetics of the opioids in adults. Adapted from Bodenham & Park (1988)

Drug	Vd_{ss} (L/kg)	CL (L/kg/h)	$t_{½\beta}$
Morphine	3.2	0.90	2.9
Alfentanil	0.39	0.20	1.63
Fentanyl	4.8	1.3	3.09
Pethidine (meperidine)	3.7	0.84	3.7

Abbreviations: Vd_{ss} = volume of distribution at steady-state; CL = total body clearance; $t_{½\beta}$ = elimination half-life.

child-bearing potential. In view of these facts the continued use of papaveretum in critically ill patients is illogical. Codeine is also used by some intensive care units but has been associated with the development of renal failure (Hill et al. 1991; Shelly et al. 1989).

3.2.2 Pethidine (Meperidine) Derivatives

This group comprises pethidine, phenoperidine and fentanyl and its derivatives (alfentanil and sufentanil). Pethidine is a synthetic opioid that is metabolised to norpethidine. Pethidine has atropine-like actions and norpethidine has a neuroexcitatory effect. In renal failure and after infusions this metabolite can accumulate and cause seizures (Szeto et al. 1977). Phenoperidine appears to offer no advantages over pethidine.

Fentanyl is a short-acting opiate when first used, although after prolonged infusion it may accumulate due to a change from a redistribution limitation of effect to being clearance limited (Mather 1983). It has few effects on the cardiovascular system, probably due to its lack of histamine release. The latter feature is also claimed to make it useful in the management of asthma, although this has not been proven.

Alfentanil is a very short-acting opiate, which may require administration by continuous intravenous infusion. Since its metabolites have been shown to be inactive it is particularly useful in patients with renal failure (Bodenham & Park 1988). In patients with hepatic dysfunction the elimination half-life of alfentanil may be markedly increased (Ferrier et al. 1985) and a prolonged duration of action may be seen.

Naloxone is the only available specific opiate antagonist and it has a short duration of action of approximately 20 minutes. If it is used to reverse opioid-induced respiratory depression repeated doses or an infusion may be necessary to maintain the desired effect. The dose of naloxone should be titrated as the complete reversal of opiate analgesia can result in severe pain which is difficult to control subsequently, and pulmonary oedema can be precipitated.

3.2.3 Nonsteroidal Anti-Inflammatory Drugs

Recently there has been increasing interest in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in place of or to supplement opioid analgesics (Dahl & Kehlet 1991). They may have an opiate-sparing effect and be of particular benefit for the relief of pain from bones and joints, as well as the general aches and pains associated with prolonged immobilisation. The use of these agents in the critically ill is significantly limited by their side effects which include reduced platelet aggregation, gastrointestinal haemorrhage, and deterioration in renal function (Clive & Stoff 1984).

3.2.4 Regional Anaesthesia

There have been few studies of the use of local anaesthetics in the critically ill. Accumulation of bupivacaine has been reported after liver transplantation. Plasma bupivacaine concentrations after intercostal nerve block in these patients may be within the toxic threshold. Despite the concentrations observed, no toxic effects attributable to bupivacaine were seen in this study, possibly due to the protective effects of other sedatives (Bodenham & Park 1990).

3.3 Other Drugs

3.3.1 Muscle Relaxants

Muscle relaxants are neither analgesic nor sedative agents. They should not be used without ensuring that the patient is both pain-free and unaware. They do, however, decrease sedative and analgesic requirements because they inhibit muscle spindles, thereby reducing muscle tone which may prevent spasms which cause pain (Green 1980). Their use should be restricted to certain specific indications such as during the initial stabilisation of a patient, in the management of increased intracranial pressure, when oxygenation is critical and there is a risk of barotrauma, and to stop the spasms of tetanus.

3.3.2 Antidepressant Drugs

The use of tricyclic antidepressants is increasing, particularly in those patients who are recovering from a prolonged period of critical illness. At

this time depression and sleep disturbances are common. Large doses are essential in the first few days to ensure rapid effect (Bronheim et al. 1985). Cardiovascular effects, in particular arrhythmias have not proved to be a problem, even when these agents are given parenterally. Whether the newer quadricyclic agents will have any advantages remains to be proven.

4. Sedation and Organ Failure

The pharmacology of sedative agents predicted from studies in animals, healthy volunteers and healthy patients undergoing elective surgery may not apply to critically ill patients. Alterations of function in hepatic, renal and other organ systems may result in altered drug effect and elimination. Furthermore, these pharmacological changes may not be constant in the critically ill patient (Shelly et al. 1987) and may apply not only to the principal drugs themselves but also to their metabolites, many of which may be active.

4.1 Hepatic Failure

The liver is the principal organ for drug metabolism. Although extrahepatic sites of drug metabolism exist (Bodenham et al. 1989; Park et al. 1989), these have only a small metabolic capacity. When hepatic insufficiency is present, either because of preexisting chronic liver disease or because of an acute derangement in liver function due to the critical illness, the elimination of drugs will be delayed and prolonged effects can be expected. Furthermore, in liver failure the sensitivity of the receptors in the central nervous system may also change, making patients more sensitive to sedative agents (Ferenci et al. 1984). In liver failure smaller doses of short-acting drugs are usually necessary. Once an ideal level of patient sedation has been achieved the frequency of drug administration or the infusion rate should be reduced considerably.

4.2 Renal Failure

The major pharmacological role of the kidneys is the excretion of the drug and its metabolites. With renal failure accumulation of metabolites may occur and this is particularly important if the metabolites are active. Several older opioids such as morphine have highly active metabolites and even some of the newer benzodiazepines such as midazolam have metabolites with some activity. It is not clear whether there are significant changes in receptor sensitivity in renal failure. However, the effects of sedative and analgesic drugs may be potentiated by uraemic encephalopathy. In patients with renal failure, or who are at risk of developing renal failure, the use of agents which do not have active metabolites is preferable. Propofol is a satisfactory sedative and alfentanil is currently thought to be a safe analgesic agent to use in this situation. If muscle relaxants need to be used atracurium is probably the safest due to its nonenzymatic degradation. Laudanosine, a metabolite of atracurium which is active in the central nervous system, does not appear to accumulate to toxic levels (Parker et al. 1988).

4.3 Gastrointestinal Failure

The gastrointestinal tract commonly fails in the critically ill patient. Gastric stasis results in drugs pooling in the stomach, and therefore they are not absorbed and are ineffective. As the patient recovers and gastrointestinal function returns to normal then drugs may be given enterally for indications such as night sedation. Although the gut is a major metabolic organ its contribution to drug metabolism is currently not known.

4.4 Brain Failure

If sedation and/or analgesia is not provided for the unconscious brain-injured patient, painful manipulations or procedures may cause episodes of hypertension, tachycardia and increases in intracranial pressure. Thus, even if the patient is thought to be unaware, analgesia at least should be given. Sedative agents may also reduce cerebral oxygen consumption. Neuromuscular blocking agents are used in combination with analgesia to prevent coughing and straining. In patients with intracranial pathology, sedation and the Glasgow coma score

should be monitored to quickly detect any deterioration in neurological condition.

5. A Practical Approach to Sedation and Analgesia

During the initial period of resuscitation, when tracheal intubation and vascular monitoring lines are being established, a short period of muscle relaxation and an adequate depth of anaesthesia are required. After this period most patients can be managed by sedation and analgesia alone. The most commonly used analgesic agent is morphine and this can be given intravenously in small incremental doses (2.5mg). An infusion can be started if this dose is required to be given frequently. For sedation and anxiolysis a short-acting benzodiazepine such as midazolam can be added using the same regimen of dosing as described for morphine. Once an infusion of either drug is started then its need should be reviewed on a daily basis and its dose reduced or discontinued until the patient is seen to recover from the effects of the drug. The infusion can be restarted, possibly at a lower dose. Apart from possibly avoiding haemodynamic instability, unnecessary use of infusions has no advantages and may induce tolerance (McQuay et al. 1981; Shelly et al. 1991). Scoring of the level of sedation is essential irrespective of the method used. In this way these drugs can be used effectively without the need for antagonists such as flumazenil and naloxone.

In those units that are less well staffed the newer agents, propofol and alfentanil, offer significant advantages. In this case a rational approach to sedation would be to start with a continuous intravenous infusion of both propofol and alfentanil. If a prolonged period of ventilatory support is anticipated and the patient does not have renal or hepatic impairment, this could then be changed to continuous infusions of midazolam and morphine. As the patient's condition improves and weaning from ventilatory support is anticipated, the morphine and midazolam infusions can be discontinued and an infusion of propofol and/or alfentanil restarted. This allows any prolonged effects of midazolam and morphine to wear off. Such a regimen is effective both in terms of patient comfort and the cost of expensive drugs.

6. Conclusion

There is no universal sedative regimen that is acceptable for all critically ill patients. The regimen should be tailored to the patients' expectations and requirements especially since their condition may change rapidly. Regular review of the drugs used and their method of administration is essential. This is common practice with all other drugs and should become so for sedative and analgesic agents when used in this patient group.

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