ANALGESIA AND SEDATION IN INTENSIVE CARE

A. R. AITKENHEAD

Most patients admitted to an intensive care unit (ICU) require analgesia, sedation or both during at least part of their stay. However, the methods used to achieve these are often determined by tradition and convenience rather than by the needs of the patients, who are exposed to a number of noxious stimuli. These include relatively constant factors such as pain after trauma or surgery, distress and discomfort from the presence of a tracheal tube and mechanical ventilation, environmental noise, and anxiety from appreciation of the severity of the illness. In addition, intermittent stimuli occur during physiotherapy, tracheal suction and nursing procedures such as turning and changing of dressings.

ASSESSMENT OF NEED

The relative requirements for sedation and analgesia depend on the presenting condition, the severity of illness and the intensity of treatment. Clearly, some type of analgesia is required for patients who have suffered trauma or undergone surgery, and opioids may be useful to suppress the cough reflex and respiratory drive in those who require tracheal intubation and mechanical ventilation. In addition, sedative agents may be necessary to allay anxiety. Sedatives may also be appropriate alone in some categories of patient, for example those with primary respiratory failure or neuromuscular disease. In patients with cerebral pathology and intracranial hypertension, sedative drugs may form a part of therapy, but in most patients sedation and analgesia are provided primarily to ensure comfort, and side effects or interactions with other drugs may produce undesirable consequences.

Few studies have attempted to identify the need for sedation in ICU patients. In general, attitudes towards sedation are influenced by three factors.

Informed anecdote

Several nursing and medical personnel who have been patients in an ICU have described their experiences [18, 49, 57]. The most notable features of these recollections are pain, anxiety and disorientation. The use of neuromuscular blocking drugs caused particular concern. However, it is possible that the existing knowledge of nursing or medical staff may have influenced their fears and anxieties.

Subjective impressions

Follow-up of ICU patients has also demonstrated that many patients experience pain and discomfort as a result of inadequate sedation and analgesia [6, 34, 36]. Bion [6] interviewed 60 patients after their discharge from a general ICU and the results of his study are shown in table I. The commonest recollections were of physiotherapy and of the presence of a urinary catheter, although these were not found to be particularly distressing by the majority of patients. Anxiety was the most commonly reported unpleasant phenomenon, but 67% of patients recalled thirst, and 60% of these found it moderately or very

<table>
<thead>
<tr>
<th>Experience</th>
<th>Percentage who recalled experience</th>
<th>Percentage who found experience unpleasant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>55</td>
<td>78</td>
</tr>
<tr>
<td>Pain</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>Lack of rest</td>
<td>45</td>
<td>63</td>
</tr>
<tr>
<td>Thirst</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Tracheal tube</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>Face mask</td>
<td>67</td>
<td>52</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>75</td>
<td>33</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>75</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Paralysis</td>
<td>13</td>
<td>100</td>
</tr>
</tbody>
</table>

TABLE I. Recall of distressing experiences by 60 ICU patients. (Adapted, with permission, from Bion [6])

A. R. AITKENHEAD, M.D., F.F.A.R.C.S., University Department of Anaesthesia, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH.
unpleasant. Pain, lack of rest, the presence of a tracheal tube and application of a face mask were also found to be unpleasant by the majority of patients who recalled these stimuli. Only two patients remembered being paralysed, but both found it unpleasant.

Bion also related the accuracy of patients' recollections to time, the drugs received and the severity of illness. Patients tended to have a poor recollection of the early part of their admission. Midazolam reduced significantly the accuracy of recall, and recollection was impaired to some extent in patients with a high APACHE II score [39] at the time of admission.

**Objective assessment**

There is at present no satisfactory objective measure of sedation or analgesia in the ICU patient other than regular clinical assessment of the patient (see below). Changes in arterial pressure and heart rate are likely to be inaccurate indices of sedation because of the effects of the patient's illness on these parameters, although they may indicate the reflex response to acute intermittent stimuli. Plasma catecholamine concentrations have been used to assess the magnitude of response to noxious stimuli during anaesthesia [15]. Concentrations of both adrenaline and noradrenaline are substantially higher than normal in ICU patients who are deeply sedated as judged by clinical criteria, and increase significantly during chest physiotherapy [2], a stimulus which is known also to increase arterial pressure, heart rate and intracranial pressure [26].

**FACTORS WHICH INFLUENCE DRUG REQUIREMENTS**

The requirement for pharmacological sedation may be reduced by a number of factors. The severity of the patient's illness may influence the dosage of analgesics necessary to achieve adequate sedation. In patients with a high APACHE II score, deeper levels of sedation are achieved at lower plasma morphine concentrations than in patients who have less physiological disturbance [8].

Frequent communication and reassurance can do much to allay anxiety, and are essential in every patient. The importance of communication by staff was highlighted by the report [49] of a former ICU nurse who, after discharge as a patient in an ICU, drew attention to the fear and anxiety associated with even the most minor procedure carried out by staff without prior explanation. Although the staff had tried hard to provide information about the time of day, the date and the month, she found that her memory span was short, and found herself frequently disorientated.

Lack of windows in an ICU deprives patients of the normal day-night cycle and of information on seasonal and weather changes; the incidence of delirium in ICU patients is more than doubled if they are managed in a windowless room [67].

Intermittent mandatory ventilation reduces the discomfort and distress associated with mechanical ventilation by permitting the patient to take spontaneous breaths on demand. Moderate hypocapnia reduces respiratory drive and improves tolerance of mechanical ventilation. Nasotracheal intubation is tolerated better than orotracheal intubation by most patients. Insertion of i.v. or intra-arterial cannulae causes pain and distress which may be obviated by the use of infiltration with local anaesthesia.

**IDEAL LEVEL OF SEDATION**

In a survey of the sedative techniques used in ICUs during 1978–79 [43], Merriman reported that 68% of units regarded the ideal level of sedation as that at which the patient was completely detached from the environment and was woken only occasionally; an even higher percentage regarded this level as ideal for patients who were very ill. However, in a larger survey conducted in 1986, Bion and Ledingham [7] found that physicians in 69% of units believed that patients should be maintained "asleep, but easily rousable". Excessive sedation with most of the available drugs leads to prolonged recovery times. In addition, large doses of i.v. anaesthetic

**TABLE II. Scoring system for assessment of sedation in ICU patients [52]**

<table>
<thead>
<tr>
<th>Level</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious, and agitated or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Co-operative, orientated and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Asleep, but brisk response to glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Asleep, sluggish response to glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>No response</td>
</tr>
</tbody>
</table>
agents [64] or opioids [64] appear to reduce immunocompetence and may be associated with an increased risk of infection.

The Glasgow Coma Score [62] is unsuitable for ICU patients. It was designed to assess patients with neurological deficit. In ICUs, limbs may be immobilized by splints or pain and the verbal responses impossible to elicit because of the presence of a tracheal tube. Linear analogue scores completed by nurses are of unproven accuracy in controlling analgesic and sedative drugs; analgesia, anxiety and sedation must be assessed separately and, although the technique may be useful for investigative purposes, it is probably not appropriate for routine use.

Ramsay and colleagues [52] described a six-point sedation score which is of practical value in a general ICU (table II). In most patients, adjustment of doses of sedative drugs to maintain a level between points 2 and 3 on their scale is desirable. This ensures that the patient is comfortable, and minimizes the risks of prolonged sedation and respiratory depression when administration is discontinued. However, additional intermittent doses of sedative or analgesic drugs are more likely to be necessary during physiotherapy or nursing procedures if patients are maintained at this level of sedation.

Electrical or mechanical monitoring of conscious level is expensive and relatively insensitive. The cerebral function analysing monitor [42] displays a processed electroencephalogram (EEG) as the mean, 10th and 90th centiles of EEG amplitude distribution, together with the relative distribution of EEG frequency in the beta, alpha, theta and delta bands (fig. 1). Increased beta activity is associated with arousal, but the distribution of frequencies during sedation varies with the drug group used. Burst suppression may be detected by an increase in breadth of the amplitude distribution. The CFAM is influenced also by sepsis [35] and by pathological coma.

The frequency of spontaneous oesophageal contractility and the amplitude of secondary oesophageal contractions increase during stress, and tend to be decreased by analgesic, sedative and anaesthetic agents [22]. Measurement of lower oesophageal contractility has been used to monitor and control the sedation of ICU patients [23], but there is considerable interindividual variability in the response of the oesophagus to anaesthetic drugs [21] and the technique has not been proved to be a useful monitor in the ICU.

**METHOD OF ADMINISTRATION**

Most sedative and analgesic drugs are administered parenterally in the ICU. Sedation is achieved most satisfactorily by continuous i.v. infusion, a technique which avoids the peaks and troughs of analgesia and sedation associated with the use of intermittent i.m. or i.v. administration. The rate of infusion should be tailored to the patient's requirements, and usually requires adjustment from time to time. It is usually preferable to initiate sedation with a relatively rapid infusion, rather than by a bolus dose which may result in undesirable cardiovascular depression. In addition, it is often necessary to supplement the basal infusion with small increments of a rapidly acting agent (e.g. i.v. anaesthetic, fentanyl or alfentanil).
or with an inhalation anaesthetic before painful procedures; this is of importance particularly in patients with intracranial hypertension, in whom painful stimulation may cause an acute and dangerous increase in intracranial pressure secondary to arterial hypertension, coughing and straining.

Other routes of administration may be appropriate in some patients. In general, the oral route is unsatisfactory because many drugs undergo extensive first-pass metabolism in the gut wall and liver, and because gastrointestinal motility is often decreased in the critically ill or postoperative patient. The buccal route is inappropriate in the patient with impaired consciousness. Rectal administration of non-steroidal anti-inflammatory drugs has been used successfully in the treatment of postoperative pain [53], and incorporation of opioids in hydrogel suppositories [27] is now being studied. The transdermal route of administration of opioids is also being investigated.

**DRUGS USED FOR ANALGESIA AND SEDATION**

**Analgesics**

Opioids are the most commonly administered drugs for sedation in ICUs. In a recent survey [7], 37% of units used an opioid drug alone for routine sedation, and a further 60% used an opioid in combination with a benzodiazepine. Opioids are appropriate for any patient in whom pain is anticipated, although the infusion rate must be titrated carefully in patients in whom artificial ventilation of the lungs is not anticipated. In the artificially ventilated patient, the antitussive action of the opioids may help toleration of a tracheal tube. The dose of opioid required is dependent in part upon the severity of the patient's illness [8]. Opioid dependence is extremely uncommon in ICU patients unless administration is continued for several days in a patient who is not in pain [43].

**Morphine**

Morphine is an appropriate drug in many situations in the ICU, although only 20% of units in the United Kingdom use it at present [7]. Its slow distribution half-life and relative lipid insolubility are disadvantages if a rapid onset of action is required, but in the patient in whom sedation will be required for many hours or several days, analgesia can be achieved by a loading dose followed by a continuous infusion. Adjustment of the dose results in a relatively slow change in level of analgesia. A loading dose of 10–15 mg followed by an infusion of 2–3 mg h⁻¹ is an acceptable initial regimen in the adult. However, as with all opioid drugs, there is enormous interindividual variation in both pharmacokinetics and pharmacodynamics, and the dose must be adjusted for each patient.

Distribution volumes and protein binding may be abnormal in the ICU patient, resulting in an exaggerated or diminished response. However, morphine is less protein-bound than other opioids. The clinical effect of alterations in hepatic function on its metabolism is small, although clinical factors which reduce hepatic blood flow, such as shock, would be expected to reduce the elimination of the drug. The main disadvantage of morphine in the ICU patient relates to the elimination of its metabolites, which are normally excreted in the urine. One of the main metabolites, morphine-6-glucuronide (M6G), is several times more active than morphine itself in animals [56]. Blood concentrations of M6G may reach high values after prolonged infusions, particularly in patients with impaired renal function [48]. Thus the infusion rate may have to be decreased after some hours, and there may be a much longer delay between cessation of the infusion and diminution of clinical effect than the elimination half-life (table III) might suggest. If very large doses have been used, respiratory depression and excessive sedation may last for more than 24 h.

In the presence of hypercapnia, the volume of distribution of morphine is decreased, and serum and brain concentrations are increased after a bolus dose of morphine [25]. In addition, the half-life of morphine in the brain is prolonged by more

<table>
<thead>
<tr>
<th>Agent</th>
<th>Distribution half-life (min)</th>
<th>Elimination half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>25</td>
<td>1.5–4</td>
</tr>
<tr>
<td>glucuronides</td>
<td></td>
<td>3–6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3</td>
<td>2–5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1</td>
<td>2–3</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>3</td>
<td>1.5–3.5</td>
</tr>
<tr>
<td>Phenoperidine</td>
<td>3</td>
<td>1.5–4</td>
</tr>
<tr>
<td>Pethidine</td>
<td>7</td>
<td>3–6.5</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>2</td>
<td>3.5–4</td>
</tr>
<tr>
<td>Buprenorphine*</td>
<td>3</td>
<td>2–4.5</td>
</tr>
</tbody>
</table>
than 50%. These differences are thought to result from acidaemia rather than hypercapnia *per se*, and a similar effect may occur in the presence of metabolic acidosis.

Morphine causes a naloxone-reversible depression of the primary immune response in mice [32]. Large doses of morphine administered for several days decrease reticuloendothelial system activity and phagocytosis in guinea pigs [40], mice and rabbits [63] and render animals more susceptible to infection. This effect is dose-related, and is not reversed by the administration of naloxone. In man, the incidences of bacterial and viral infections are high in heroin addicts [11]; these infections have been attributed in the past solely to the use of contaminated drug, syringes and needles, but may be related to the decreased macrophage numbers and activity demonstrated in small animals. It is not clear at present whether this effect, which has obvious implications in the ICU patient, is common to all opioid drugs.

**Papaveretum**

The analgesic effects of this drug are predominantly attributable to the morphine which it contains, but the other alkaloids appear to provide more of a sedative effect than morphine alone. This may be an advantage in many patients, but can result in prolonged narcosis if large doses are given, particularly to elderly patients or those with hepatic or renal impairment. Papaveretum has retained popularity as a sedative in British ICUs; it was used frequently by 32% of units in the late 1970s [43], and was the preferred opioid in 33% of units in 1987 [7].

**Fentanyl**

This drug is often thought to be superior to morphine or papaveretum because of its short duration after a single bolus dose. However, this effect is the result of its high lipid solubility, which permits rapid equilibration between blood and central nervous system. As the drug is also distributed into other tissues, blood and CNS concentrations decay within a few minutes, and its analgesic and respiratory depressant actions wane. After repeated administration of fentanyl or after prolonged infusion, blood and CNS concentrations decrease only as the drug is metabolized, because distribution into other tissues has already occurred. The elimination half-life of fentanyl is longer than that of morphine (table III) after a single bolus dose; in the elderly, the elimination half-life is extended to 9 h, and may be as long as 16 h after a prolonged infusion [54]. Consequently, fentanyl is *not* a short-acting drug when used for analgesia in the ICU, and offers little advantage over morphine.

**Alfentanil**

Alfentanil has a small distribution volume and short terminal half-life in most patients. Consequently, it should be a useful drug for administration by infusion, as changes in infusion rate should produce a rapid alteration in clinical effect. However, it is an expensive agent. Although its use has been reported as satisfactory in a small number of ICU patients [12], it had no advantages over pethidine in another study [68]. In addition, its elimination is delayed and its duration of action prolonged in some patients [68]. When a prolonged period of analgesia is anticipated, it may be appropriate to use alfentanil to establish analgesia rapidly before changing to use of another opioid; its use might also be considered towards the end of the treatment period to decrease the risks of prolonged respiratory depression when the infusion is discontinued.

**Pethidine**

Pethidine is a useful alternative to morphine, especially in patients prone to bronchospasm. It is rather more lipid soluble than morphine, and its actions are therefore of more rapid onset. At low infusion rates, it is a useful analgesic in the spontaneously breathing patient, and it possesses relatively little sedative effect. However, it depresses myocardial function in high doses, and its major metabolite, norpethidine, has convulsant properties and may accumulate in patients with impaired renal function [37]. Blood concentrations of pethidine are increased in the elderly, and its elimination is delayed in patients with hepatic dysfunction.

**Phenoperidine**

This opioid drug, which is related to pethidine, was the most commonly used in the late 1970s [43], and is still the preferred drug in 27% of British units [7]. However, there is no objective evidence that it has any advantage over other drugs. It may increase intracranial pressure [31] and its cardiovascular effects are rather more significant than those of other opioids. Phenoperidine causes peripheral vasodilatation, and arterial pressure decreases by up to 20% in non-
ICU patients [51]. Several cases of profound cardiovascular depression have been reported in ICU patients after administration of pheno- peridine [19,28].

Agonist–antagonist opioids

Buprenorphine has a slow onset and prolonged duration of action, effects related to receptor binding rather than blood concentration. Nal- buphine has a relatively rapid onset, and a half-life of 3–4 h [1]. The main advantage claimed for these drugs is their “ceiling” effect in respect of respiratory depression. However, respiratory depression can occur with either agent; after buprenorphine, it may occur some time after administration, and is resistant to antagonism by naloxone [33]. In high doses, buprenorphine may antagonize its own analgesia. There may be a “ceiling” to the analgesic as well as the respiratory effects of these drugs.

Side Effects of Opioids

Respiratory

All pure agonist opioids decrease the rate and volume of ventilation, and decrease the sensitivity of the respiratory centre to carbon dioxide. It is likely that equianalgesic doses of any pure agonist result in equivalent degrees of respiratory depression. This side effect is often advantageous during controlled ventilation. However, infusions of opioids must be controlled very carefully in the spontaneously breathing patient if significant respiratory depression is to be avoided. In the ventilated patient, residual effects of opioids on the respiratory centre may delay weaning from the ventilator. The delay is to some extent unpredictable, even with the shorter-acting agents. The rate of elimination of opioids may vary by a factor of five even in normal individuals, and impaired metabolism and excretion, together with accumulation of metabolites, may result in a very prolonged duration of action in some patients.

Cardiovascular

All opioids may decrease arterial pressure by causing arterial and venous dilatation. This effect is seen particularly in the hypovolaemic patient. In clinical doses, myocardial depression is minimal [38]. In addition, an initial decrease in arterial pressure may result from the alleviation of pain and anxiety. The use of pheno- peridine is associated with a greater decrease in arterial pressure than most other opioids. Fentanyl has less depressant effect on the cardiovascular system than morphine in patients with cardiac disease [41]. Pethidine has a vagolytic action which results in an increase in heart rate. The cardiovascular effects can be minimized by ensuring that the circulating volume is adequate, and by providing the initial loading dose as an infusion over 10–15 min rather than as a single bolus dose.

Gastrointestinal

All of the opioids delay gastric emptying and decrease intestinal motilility. This may impair the ability to absorb enteral feeds, and may increase the risks of regurgitation and aspiration of gastric contents. Spasm of the sphincter of Oddi and an increase in common bile duct pressure may occur with all opioids, but the clinical significance of this in the ICU patient is not clear; this effect is antagonized by atropine, but not by naloxone.

Tolerance and addiction

Some degree of tolerance to opioids may occur after 3–4 days, and the infusion dose may have to be increased. Tolerance to both the analgesic and respiratory depressant effects occur. Addiction, reflected by withdrawal symptoms when the drug is discontinued, is excessively uncommon in patients who receive opioids for the treatment of pain, and fear of addiction should not limit dosage adjustments if tolerance develops.

Non-Opioid Analgesics

The combination of opioid and non-opioid analgesics may decrease the dose, and thus the potential for side-effects, of opioid drugs required to produce adequate analgesia. Indomethacin suppositories decrease the need for morphine after surgery [52] and have been used successfully to supplement opioids in patients with blunt chest trauma. However, haemorrhagic complications may occur. Lysine acetyl salicylic acid can be administered parenterally, and provides good postoperative analgesia [10].

Sedatives

Sedative drugs may be used alone, or in combination with opioids, to achieve sleep and anxiolysis in the ICU patient. As long as sufficient analgesia is achieved, not all patients require sedative drugs, particularly after the first 24–48 h
of admission. It is inappropriate to use high doses of opioids alone to achieve deep sedation, as the doses required may result in prolonged respiratory depression. Similarly, it is inappropriate to use sedative agents alone for patients who are in pain, as anaesthetic doses are required. If patients have no source of pain, then sedatives may be administered alone. In most patients, however, a balanced combination of analgesic and sedative drugs titrated to individual needs results in relief of pain and anxiety, but permits continued communication with staff.

**Benzodiazepines**

These agents induce sleep, anxiolysis and a decrease in muscle tone. Although total sleep time is increased, there is a reduction in REM sleep [4]. *Diazepam* has an elimination half-life of 36 h and an active metabolite, N-desmethyl diazepam, with an elimination half-life of up to 96 h [29]. Infusion of diazepam is therefore inappropriate, and it is best administered as a loading dose with maintenance doses every 12–24 h. Recovery of consciousness may take several days if large doses are administered. Diazepam causes severe thrombophlebitis if administered into a peripheral vein, although the incidence of this complication is very low when the lipid emulsion formulation (Diazemuls) is used.

*Flunitrazepam* and *lorazepam* have long half-lives (20 and 15 h, respectively) and lorazepam also has a slow onset of action.

*Midazolam* has a rapid onset of action and a shorter duration of action in normal individuals than diazepam, flunitrazepam or lorazepam. It is water-soluble and can be administered safely into peripheral veins. Its elimination half-life in normal individuals is 2–4 h after a single dose, although this may be prolonged significantly in critically ill patients [55]. Although one of the metabolites, alpha-hydroxy midazolam, is active, it has an elimination half-life of only 1 h. Because of first-pass metabolism, alpha-hydroxy midazolam concentrations are higher after oral than after i.v. administration, and the metabolite contributes to the sedative actions of the drug [14]; however, the prolonged action of midazolam in ICU patients is likely to be the result of impaired hepatic metabolism rather than accumulation of metabolites. It may be difficult to detect clinical differences between midazolam and diazepam when administered in repeated doses [17]. In 1987, 45% of British ICUs used diazepam (as Diazemuls), and 39% midazolam [7]; lorazepam, which was popular in the late 1970s [43], is now used infrequently.

Although the benzodiazepines produce profound amnesia, they often fail to achieve satisfactory sedation. Amnesia *per se* may not prevent subsequent psychological sequelae after traumatic experiences; indeed, memory may be improved by benzodiazepines in anxious individuals [16]. All of the benzodiazepines tend to produce cardiovascular and respiratory depression. In addition, doses required to produce satisfactory sedation in the ICU patient often obliterate verbal contact with the patient and also result in significant delays in recovery if administration is prolonged.

The imidazobenzodiazepine, flumazenil, has been marketed recently as a benzodiazepine antagonist. The manufacturers recommend its use to antagonize the sedative effects of benzodiazepines to allow return to spontaneous ventilation and consciousness in patients in intensive care. However, its properties in the critically ill patient have not yet been investigated adequately. Its half-life is short and sedation and respiratory depression may recur unless an infusion of flumazenil is used for a prolonged period [9]; specific information about its half-life in the critically ill patient is limited. Rapid antagonism of sedation may result in hypertension and tachycardia. The effects of prolonged infusion of midazolam may not be antagonized at all [19]. Although flumazenil may offer a solution to the problems of prolonged recovery after benzodiazepine administration in the ICU patient, the use of antagonists to expedite recovery after therapeutic doses of drugs has inherent disadvantages, and it is the author's opinion that, in general, agonist drugs with rapid elimination and recovery are to be preferred.

**I.v. anaesthetics**

*Barbiturates.* Thiopentone and pentobarbitone are indicated occasionally in patients with severe head injury, as they help to control intracranial hypertension. However, after prolonged administration, slow elimination results in protracted coma. In moderate doses (approximately 100 mg h\(^{-1}\)) for up to 14 days, recovery of consciousness takes up to 48 h. In doses large enough to produce an isoelectric EEG, recovery may take up to 4 days [59]. Deep coma induced with thiopentone for treatment of patients with head injury has
been associated with increased incidences of sepsis and adult respiratory distress syndrome [64], possibly as a result of reduced immunological competence. Barbiturates in high doses may result in significant cardiovascular depression.

**Etomidate.** This agent was used widely for sedation in the ICU after its introduction, although no properly conducted clinical trials had been undertaken to confirm its safety during prolonged infusion. Careful audit in one unit resulted in the detection of increased mortality associated with infective complications in a group of trauma patients who had received etomidate [65]. Further investigations revealed that etomidate induces adrenocortical suppression, even after a single dose [45]. It is, therefore, entirely unsuitable as a sedative agent in the critically ill patient.

**Propofol.** This new agent is insoluble in water, and is formulated in a lipid emulsion. It has a short elimination half-life and recovery of consciousness from anaesthesia after a single bolus or short infusion is free of the “hangover” associated with the use of most other i.v. anaesthetic drugs.

Only limited information is available regarding the safety of propofol for sedation in the ICU. It has been used successfully for 2.5–18 h after cardiac surgery [30]. The use of propofol was associated with more easily controlled sedation than midazolam, and a shorter requirement for mechanical ventilation; the median time from discontinuation of the infusion to the return of spontaneous ventilation was 9.5 min after propofol and 202 min after midazolam. A pilot study [47] in which propofol was used for 8 h in 10 ICU patients confirmed that the drug was useful and readily controllable as a sedative agent, but noted that critically ill patients might be particularly sensitive to the cardiovascular depressant properties of the drug.

In a recent multicentre study [Aitkenhead AR and colleagues, in preparation] 101 patients were allocated randomly to receive either propofol or midazolam, in combination with a continuous infusion of morphine 2 mg h⁻¹, for up to 24 h. The level of sedation was adjusted easily during infusion of propofol 1–3 mg h⁻¹, and communication was maintained with the patients (Ramsay scale points 2 or 3 (table II)). Consequently, there was no difference between midazolam and propofol in respect of recovery of consciousness, but propofol was superior in a subgroup of patients observed for recovery to the point at which weaning from artificial ventilation could be considered. Decreases in arterial pressure did occur with propofol, but were not significantly different from those caused by midazolam and responded to i.v. fluid infusion; it was never necessary to discontinue the administration of propofol because of side effects. Heart rate was slower with propofol. There were no biochemical abnormalities attributable to either drug. Although cortisol concentrations decreased during the infusion of both drugs, there was no inhibition of the Synacthen test. The lipid solution was not associated with any adverse effects.

In a small number of ICU patients who received propofol because of severe agitation, there appeared to be minimal accumulation of the drug over a 4-day period, and recovery times, which were assessed every 24 h, remained rapid (< 30 min) [5]. However, it must be stressed that experience with this agent is limited. The drug is cleared more slowly in the presence of renal insufficiency [46] and the safety of infusion for longer than 24 h has not been established.

**Chlormethiazole.** This drug is used occasionally to sedate ICU patients. It produces little cardiovascular depression, and may increase heart rate and arterial pressure. However, it is formulated for i.v. use in a dilute solution, and large volumes are required to provide sedative doses. It is metabolized slowly in patients with hepatic dysfunction, and this may result in prolonged recovery of consciousness. Nevertheless, some units find it to be satisfactory in selected patients.

**Ketamine.** This drug has analgesic properties at subanaesthetic doses (0.5 mg kg⁻¹). However, its use as a sedative has been disappointing except in patients with severe bronchospasm, in whom it has been used successfully [60].

**Inhalation anaesthetic agents**

Virtually all of the inhalation anaesthetic agents have been used to produce sedation in the ICU. Not all possess analgesic activity at subanaesthetic concentrations. **Nitrous oxide** is useful in providing intermittent analgesia, for example during physiotherapy or other painful procedures. Concentrations up to 70% have been used, but may be limited by the requirement of the patient for a
high inspired oxygen concentration. Prolonged use of nitrous oxide is associated with megaloblastic bone marrow changes [3]. Enflurane and isoflurane have also been used, but there have been no adequate investigations of the use of these agents for prolonged periods. Adequate scavenging facilities must be provided if inhalation agents are used.

Neuromuscular Blocking Drugs
A study published as recently as 1980 [44] showed that pancuronium was administered to "calm" 48 of 50 ventilated patients, and that it was by far the most commonly used drug for encouraging patients to tolerate artificial ventilation, in some cases without any sedation or analgesia. Thirty-one of 34 units surveyed in 1978–79 claimed to use pancuronium frequently, and a number of units used curare [43]. A subsequent editorial [20] drew attention to the dangers of paralysis in the conscious patient. Although nurses often prefer patients to lie still, and equate immobility with sedation, there are several important sequelae. Most distressing to the patient is awareness of pain, distress and paralysis [49]. In addition, the risk of hypoxaemia resulting from accidental disconnection from the ventilator is increased, pulmonary emboli are more frequent [61], the cough reflex is suppressed totally and peripheral nerve injury from incorrect positioning may occur [66].

Fortunately, the warnings have been heeded, and it is now uncommon for neuromuscular blocking drugs to be used in the ICU; only 16% of units surveyed in 1986 used them, 71% of these only rarely [7]. However, they are still indicated in some circumstances. In patients with severe hypoxaemia, oxygenation may be improved by using a neuromuscular blocker if chest wall compliance is increased, particularly if the patient is restless. In patients with intracranial hypertension, improved control of intracranial pressure may be achieved by neuromuscular blocking agents, probably because of an increase in venous capacitance secondary to a decrease in skeletal muscle tone. Muscle relaxants may be required also in patients with tetanus. Irrespective of the indication, it is essential to ensure that the patient is adequately sedated before any neuromuscular blocking drug is given.

Pancuronium achieved popularity in the ICU because of its tendency to increase arterial pressure. However, it also induces a tachycardia, and this may be a disadvantage in patients who may already have an increased heart rate as a result of disease. Vecuronium and atracurium have little effect on the cardiovascular system. However, vecuronium may accumulate in the critically ill patient [58], leading to prolonged paralysis. Atracurium is probably preferable if a neuromuscular blocking drug is indicated. A recent case report suggests that accumulation of the major metabolite laudanosine is minimal even after infusion of atracurium for 71 days [50], although concern has been expressed that laudanosine might accumulate in patients with renal insufficiency [24].

Regional Analgesia
Some patients in ICU may benefit from regional anaesthetic or analgesic techniques, although the presence of sepsis or coagulation defects are contraindications to the major regional techniques. Extravascular administration of local anaesthetic drugs may result in unacceptable hypotension in the presence of hypovolaemia. In selected patients the administration of local anaesthetic drugs by continuous slow infusion provides analgesia with little cardiovascular depression, and may be of value in the patient with poor respiratory reserve after abdominal or thoracic surgery, or after blunt chest trauma. Extravascular opioids may result in good analgesia without cardiovascular depression [13]; lipid soluble drugs such as fentanyl or diamorphine are more effective, and are associated with a lower incidence of respiratory depression than insoluble agents, for example morphine.

When appropriate, other local anaesthetic techniques such as brachial plexus or intercostal block may be used; the use of an indwelling catheter allows prolonged block to be achieved.

CONCLUSION
Sedation in the ICU must be tailored to the needs of each patient. The appropriate use of analgesic drugs or techniques may be used together with methods of reducing psychological stress to minimize the administration of sedative agents, thereby retaining verbal contact with the patient. The risks of delayed recovery of orientation and respiratory drive are decreased by avoiding excessively deep levels of sedation, and by using
drugs which are metabolized and eliminated rapidly.

REFERENCES


68. Yate PM, Thomas D, Short SM, Sebel PS, Morton J. Comparison of infusions of alfentanil or pethidine for sedation of ventilated patients on the ITU. *British Journal of Anaesthesia* 1986; 58: 1091–1099.