

# Comparative Tolerability of Sedative Agents in Head-Injured Adults

Susan C. Urwin<sup>1</sup> and David K. Menon<sup>2</sup>

1 Department of Anaesthesia, Addenbrooke's Hospital, Cambridge, United Kingdom

2 Department of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom

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## Abstract

Sedative agents are widely used in the management of patients with head injury. These drugs can facilitate assisted ventilation and may provide useful reductions in cerebral oxygen demand. However, they may compromise cerebral oxygen delivery via their cardiovascular effects. In addition, individual sedative agents have specific and sometimes serious adverse effects. This review focuses on the different classes of sedative agents used in head injury, with a discussion of their role in the context of clinical pathophysiology. While there is no sedative that has all the desirable characteristics for an agent in this clinical setting, careful titration of dose, combination of agents, and a clear understanding of the pathophysiology and pharmacology of these agents will allow safe sedative administration in head injury.

Sedation in any intensive care setting is used to provide anxiolysis, amnesia and to relieve agitation. In head-injured patients undergoing mechanical ventilation, sedation enables the manipulation of respiration, which may be essential in the treatment of raised intracranial pressure (ICP). Sedative agents are also an intrinsic part of the treatment of raised ICP because of their actions on cerebral metabolic rate (CMRO<sub>2</sub>) and cerebral blood flow (CBF). Pain relief may also be required, usually by the addition of an intravenous opioid, which has an additive effect on the sedative agent used. The purpose of this review is firstly to discuss the pathophysiology of head injury, then to discuss the sedatives available for the treatment of adult head-injured patients. It is important to make two additional points.

First, the use of sedative agents in head-injured patients should be viewed as part of their overall management. Such management is ideally based on guidelines that have been provided by the Brain Trauma Foundation and the American Association of Neurological Surgeons.<sup>[1]</sup> While these guidelines provide comprehensive evaluation of the scientific basis of clinical head injury management in many areas, guidance on sedative use is limited, with the exception of barbiturate use for refractory intracranial hypertension.

Second, much of the scientific basis for making decisions regarding sedative use in this context derives from studies in the operating theatre setting. While such data are extremely valuable, they cannot

always be directly extrapolated to provide a foundation for intensive care practice. Results from studies in the operating room are usually 'contaminated' by the use of other anaesthetic drugs. On the other hand, the critical care scenario may be confounded by other factors. Extracranial injuries may alter haemodynamic responses, organ dysfunction may substantially delay drug elimination, and concomitant drug treatment can result in pharmacokinetic interactions. Perhaps most importantly, the duration of sedation in the intensive care unit (ICU) setting (days to weeks) may result in problems that would not be detectable, even with long anaesthesia-based studies, which last hours.

A recent position paper from the Society of Critical Care Medicine<sup>[2]</sup> provides valuable guidelines on the sustained use of sedatives and analgesic agents in critically ill adults. Unfortunately, although the paper contains a useful discussion of the pharmacology of many of the agents used, it provides little specific guidance regarding such treatments in the head-injured population. In particular, there is no discussion on the titration of sedative agents in patients with neurological injury, in whom standard sedation scales are inappropriate.

## 1. Pathophysiology in Head Injury

The effects of head injury occur not only in the CNS,<sup>[3]</sup> but are widespread throughout many body systems.

### 1.1 Pathophysiology: Secondary Neuronal Injury and Cerebrovascular Homeostasis

Damage to the CNS due to head injury can be divided into the primary and secondary injury. The primary injury occurs with the initial impact and is caused by direct damage, flexion, extension and shearing forces. These insults may cause diffuse axonal injury, cerebral oedema and intracranial haematomas, leading to raised ICP, a reduction in cerebral perfusion pressure (CPP), and cerebral ischaemia. Secondary damage occurs after the initial trauma as a result of insults such as hypoxia, hypercapnia, systemic hypotension and intracranial hypertension. It is these derangements that appropriate resuscitation and subsequent intensive care management aim to avoid. Secondary damage occurs due to a number of processes at the subcellular level. These include accumulation of excitatory amino acids (EAA) that cause accumulation of intracellular calcium ions by their action on *N*-methyl-D-aspartate (NMDA) receptors,<sup>[4]</sup> phospholipase activation,<sup>[5]</sup> free radical generation and lipid peroxidation.<sup>[6]</sup>

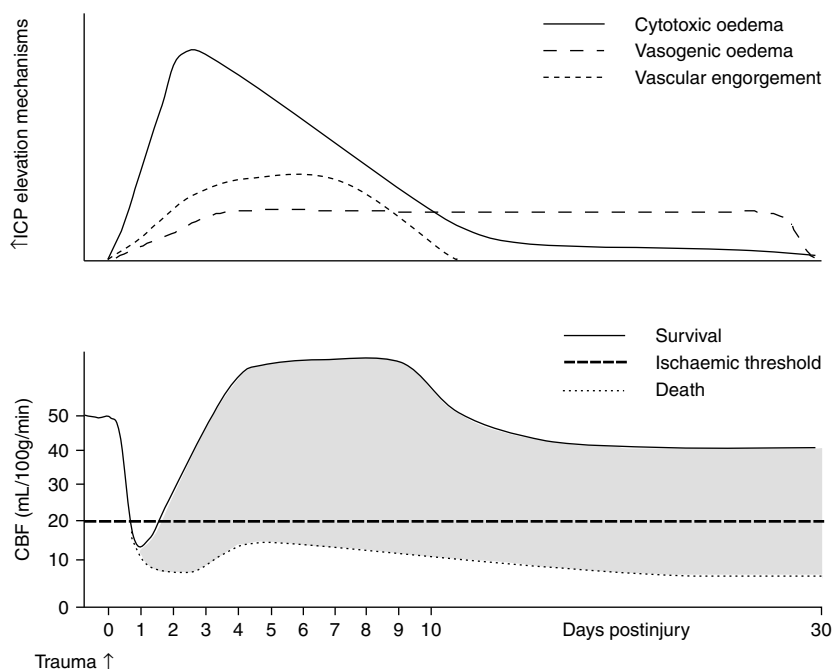
There is an intimate and continuing interplay between the various steps of the cascade described above.<sup>[3]</sup> Un-evacuated intracranial haematomas may not only raise ICP and worsen cerebral hypoxia, but may also be responsible for the activation or intensification of EAA release, inflammation and microvascular dysfunction. The microvascular dysfunction, in turn, may limit the ability of the injured brain to cope with minor variations in physiology. Indeed, while the normal brain has the autoregulatory capacity to cope with mild hypotension that results in CPP reduction to 50mm Hg, it has been well documented that patients with acute head injury, as a group, tend to require CPP values above 60–70mm Hg in order to maintain cerebral perfusion (see later in this section). Further, at later stages after head injury, the presence of extravascular blood may predispose to large vessel spasm, with the potential for distal hypoperfusion and ischaemia.

The varied pathophysiological consequences of a single structural pathology are well reflected by sequential changes in cerebrovascular physiology that are observed following head injury. Classically, CBF is thought to show a triphasic behaviour (figure 1).<sup>[7]</sup> Soon after head injury (<12 hours), global CBF

is reduced, sometimes to ischaemic levels. Between 12 and 24 hours post-injury, CBF increases, and the brain may exhibit supranormal CBF. Many reports refer to this phenomenon as hyperaemia, and CBF levels may be inappropriately high for metabolic needs in many patients beyond the first 24 hours after head injury. However, some patients may not exhibit reductions in cerebral oxygen extraction, suggesting that metabolism and blood flow often remain coupled, and a more appropriate label in these patients would be hyperperfusion. CBF values begin to fall several days following head injury, and in some patients these reductions in CBF may be associated with marked increases in large vessel flow velocity on transcranial Doppler ultrasound, which suggest vasospasm.

These time-varying haemodynamic responses also define the vascular contribution to ICP elevation in time.<sup>[3]</sup> Immediately after head injury, there is no vascular engorgement, and although a transient blood-brain barrier (BBB) leak has been reported in the immediate period after impact in animals, there is no evidence of BBB disruption at this stage in humans. Apart from surgical lesions (e.g. intracranial haematomas), ICP elevation during this phase is often the consequence of cytotoxic oedema, usually secondary to cerebral ischaemia. Increases in CBF and cerebral blood volume (CBV) from the second day post-injury onward make vascular engorgement an important contributor to intracranial hypertension. The BBB appears to become leaky between the second and fifth days post-trauma, and vasogenic oedema then contributes to brain swelling. If these patterns were consistent and predictable, they would allow the rational selection of treatment at each stage following trauma. Unfortunately, patients vary enormously, and different mechanisms responsible for intracranial hypertension may operate concurrently, even within a single individual at any given time point. However, the discussion above does apply to groups, and provides a useful basis on which to select initial 'best guess' therapy in an individual patient, especially when data from multimodality monitoring are also available to help guide treatment choices.

The ability of the cerebral circulation to maintain CBF at a relatively constant level in the face of changes in CPP by altering cerebrovascular resis-



**Fig. 1.** Schematic diagram of cerebral blood flow (CBF) responses following closed head injury (lower panel). The upper panel shows the relationship of these changes to pathophysiological mechanisms responsible for intracranial hypertension, with ischaemic cytotoxic oedema contributing at early time points, and vascular engorgement and vasogenic oedema due to blood-brain barrier leak contributing later (reproduced from Bullock<sup>[8]</sup> with permission). **ICP** = intracranial pressure.

tance (CVR) is termed autoregulation (figure 2).<sup>[9]</sup> In normal circumstances, as both ICP and cerebral venous pressure are low, systemic arterial perfusion pressure becomes the primary determinant of CPP. In pathological states, however, ICP becomes a significant factor in determining CPP. Autoregulation has limits above and below which CBF is directly related to perfusion pressure. Above the higher limit of autoregulation, increases in mean arterial pressure (MAP) lead to forced dilatation of cerebral arterioles, an increase in CBV, disruption of the BBB and formation of cerebral oedema, with a resultant increase in ICP. Below the lower autoregulatory limit, CBF falls linearly with decreasing perfusion pressure. Brain injury is known to disrupt autoregulation in many patients. In this setting, changes in MAP modulate cerebral perfusion at levels that would normally be associated with preservation of CBF at constant levels. Intensive care management of head-injured patients therefore focuses on minimising the ICP and maintaining the CPP. It has been well reported that intracranial

hypertension is associated with a poor outcome following head injury,<sup>[10-12]</sup> and evidence suggests that cerebral autoregulation is preserved when CPP is kept above 60–70 mm Hg,<sup>[13-15]</sup> with recent evidence favouring the lower of these two figures.<sup>[16]</sup> Local mechanisms for the control of CBF are also disturbed following head injury, leading to altered coupling between CBF and metabolic demands. Clinical studies suggest an initial severe reduction in CBF in the first 3–8 hours after head injury, followed by a gradual increase until metabolic demands are met.<sup>[17-20]</sup> The level of cerebral metabolism, the preservation of flow metabolism coupling, and the efficiency of autoregulation are crucial issues in predicting the effect of sedation on cerebral blood flow and intracranial pressure. Agents that reduce cerebral metabolism may be beneficial in head injury for two reasons. First, they may reduce oxygen demands in the setting of limited oxygen delivery. Second, these reductions in cerebral metabolism will be coupled to reductions in CBF when flow-metabolism coupling is preserved. Since such

CBF reductions are accomplished by reductions in vascular calibre, this will result in reductions in cerebral blood volume, and (especially in patients with a non-compliant intracranial cavity), consequent reductions in ICP and increases in CPP. However, these benefits may be substantially attenuated or absent if baseline metabolism is low and not suppressible by depressant drugs, e.g. in the setting of an isoelectric or burst-suppressed electroencephalogram (EEG), or if flow metabolism coupling is deranged (as in hyperaemia). Under such circumstances, the dominant effects may be due to cardiovascular depression, which is a recognised adverse effect of most sedative agents. This may result in MAP reduction below autoregulatory thresholds and result in reductions in CBF. MAP reduction may also trigger autoregulatory vasodilatation and result in increases in CBV and ICP.

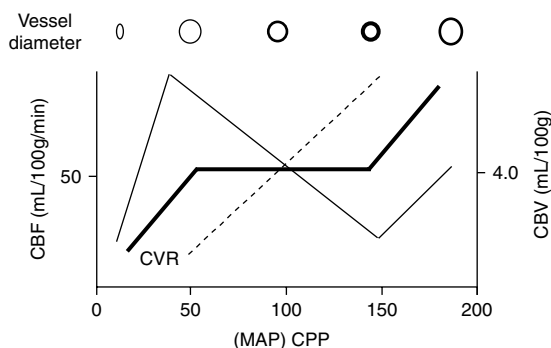
## 1.2 Extracranial Injury – Pathophysiology and Clinical Impact

The effects of sedative agents on cardiorespiratory function are further enhanced by extracranial injuries, or by complications that directly result from head injury. A study of 734 patients with severe head injury showed that electrolyte distur-

bances were the most frequent complication, occurring in 59% of patients, followed by pulmonary infections (41%), shock (29%), coagulopathy (19%) and septicaemia (10%).<sup>[21]</sup> Haemodynamic abnormalities<sup>[22,23]</sup> and dysrhythmias<sup>[24,25]</sup> are common following head injury, and overt myocardial damage was shown to occur in up to 50% of head-injured patients in the absence of coronary artery disease.<sup>[26]</sup> These abnormalities sensitise patients to the cardiovascular depressant effects of common sedative agents. Further, abnormal autonomic responses following head injury<sup>[27,28]</sup> may result in exaggerated or unusual responses to sedation and its associated attenuation of sympathetic activity. Tracheal intubation and/or ventilatory support are often required in severe head injury because of depressed airway reflexes, hypoventilation, or the development of aspiration pneumonia or neurogenic pulmonary oedema.<sup>[29-32]</sup> Ventilation to mild hypocapnia, with or without neuromuscular blockade, may also be required for ICP control. These factors necessitate the use of sedative agents to facilitate ventilation, since patients who exhibit substantial ventilator asynchrony may suffer substantial increases in intrathoracic pressure (and hence ICP). Patients who receive neuromuscular blocking agents usually receive intravenous benzodiazepines or anaesthetic agents in Europe, but it is not uncommon for such patients to receive only opioids in the US. There are no systematic investigations of the risks of awareness in such patients, but there is no suggestion that this is a problem, even in those patients who receive opioids as their sole sedative agent.

In many patients with severe head injury, gastric emptying is delayed, and this may persist for up to 2 weeks after traumatic head injury.<sup>[33]</sup> Delayed gastric emptying may be a direct consequence of raised ICP.<sup>[34]</sup> This may be more of a problem with more severe head injury,<sup>[35]</sup> and may be due to activity of inhibitory vagal pathways that reduce the amplitude of gastric contractions.<sup>[36]</sup>

Although at least one study showed no improvement in gastric emptying as a result of withholding morphine in head injury,<sup>[34]</sup> it is generally felt that sedative and analgesic agents (particularly opioids) can further exacerbate this problem. Impaired gastric emptying may delay the establishment of enteral nutrition; this may result in malnutrition, a need to



**Fig. 2.** Pressure autoregulation. A change in cerebrovascular resistance in the face of changes in cerebral perfusion pressure to maintain cerebral blood flow (CBF). Note that cerebral vasodilatation and thus a decrease in cerebrovascular resistance (CVR) maintains CBF, with reductions in cerebral perfusion pressure. This increases cerebral blood volume (CBV), which results in critical increases in intracranial pressure in patients with poor intracranial compliance. The process is reversed with elevation of cerebral perfusion pressure (CPP), and increases in mean arterial pressure (MAP) may induce reductions in intracranial pressure due to reflex vasoconstriction in patients with preserved cerebrovascular pressure autoregulation.

**Table 1.** Characteristics of an ideal sedative agent

Good quality sedation
Rapid onset and offset of action
Non-cumulative
No systemic adverse effects
Inexpensive
In addition to these properties, a sedative used on the neurointensive care unit should also:
Maintain cerebral autoregulation and cerebrovascular response to PaCO <sub>2</sub>
Reduce CMRO <sub>2</sub> , to an extent that provides an isoelectric or burst-suppressed EEG
Reduce CBV and hence ICP
Reduce seizure activity
Have rapid offset of action to enable neurological assessment
Result in rapid changes in CNS depression in response to changes in dose
<b>CBV</b> = cerebral blood volume; <b>CMRO<sub>2</sub></b> = cerebral metabolic rate; <b>EEG</b> = electroencephalogram; <b>ICP</b> = intracranial pressure; <b>PaCO<sub>2</sub></b> = partial carbon dioxide pressure.

resort to parenteral nutrition, and/or a perceived requirement for prophylaxis against stress ulceration.<sup>[37]</sup>

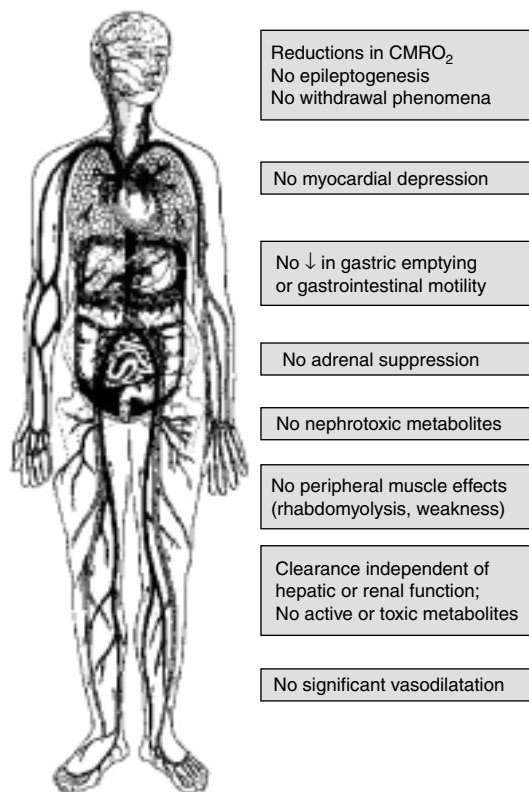
## 2. Overview of Sedative Agents

### 2.1 Context for Use of Sedation in Head Injury

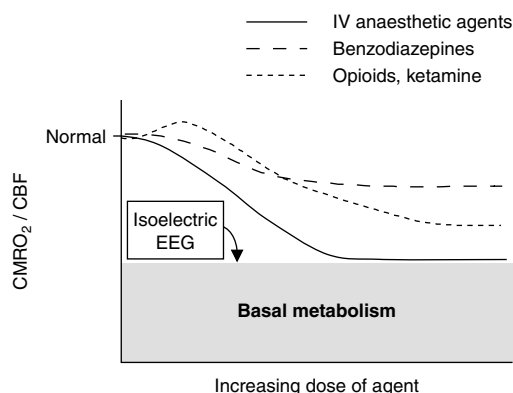
Following head injury, sedation may be instituted in emergency situations in the pre-hospital phase. More commonly, it is instituted in the Accident and Emergency Department, usually to allow airway control. Continued use may be required in the short term, e.g. to allow an agitated patient to undergo radiological imaging. It may be required in the longer term on the neurocritical care unit (NCCU). Sedation on the NCCU is required to provide the amnesia, anxiolysis and compliance with treatment that is required on any intensive care unit. In addition, it may represent an intrinsic part of the management of the head-injured patient, by reduction of cerebral metabolism, with coupled reductions in CBV and hence ICP. Such agents may also be required for the control of refractory acute post-traumatic epilepsy.

### 2.2 Properties of the Ideal Sedative Agent

The concept of the 'ideal' sedative agent must be modified for use on the NCCU. Traditional properties of the ideal sedative, and the additional demands made by neurointensive care are specified in table I and figure 3. Perhaps more so than in any other critical care setting, there is a need for ease of ability to titrate for sedation in head injury. Such patients may require rapid increases in levels of sedation to cover clinical procedures or other stimuli, which could result in dangerous ICP elevations if left untreated. Some patients may require high doses of sedatives to achieve metabolic suppression. Indeed, several of the drugs that we use can not produce such profound metabolic suppression, and it is important to understand the pharmacodynamic profiles



**Fig. 3.** Desirable organ-specific effects of the ideal sedative agent. Several organ systems may be compromised by extracranial injury and by the pathophysiological consequences of head injury, making patients more susceptible to unwanted effects of sedative agents. **CMRO<sub>2</sub>** = cerebral metabolism; ↓ = decrease.



**Fig. 4.** Schematic diagram showing the effect of different sedative agents on cerebral metabolism ( $\text{CMRO}_2$ ) and coupled cerebral blood flow (CBF). It demonstrates the 'ceiling' effect on these parameters of benzodiazepines and opioids. Barbiturates and other anaesthetics, in sufficient doses, will reduce metabolism to a point where the electroencephalogram (EEG) is isoelectric and metabolism has been reduced to basal levels. IV = intravenous.

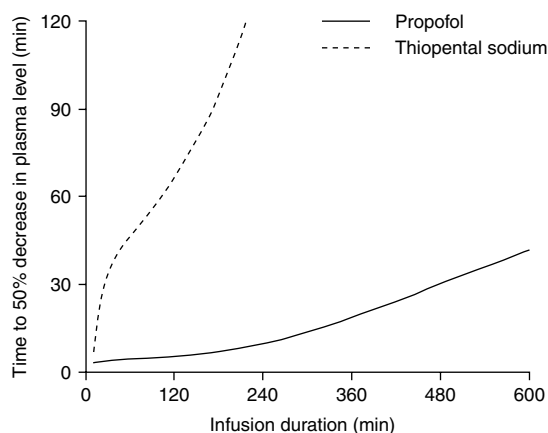
of the agents commonly used in this setting (figure 4).

On the other hand, there may be a clinical need to achieve a rapid reversal of sedation to enable neurological assessment, and it would be highly desirable to be certain that a depressed conscious level after cessation of sedation was not the consequence of residual effects of the drugs used. These considerations underline the need for drugs that not only have a rapid onset, but also a rapid offset. Commonly used agents, such as thiopental sodium (thiopentone) and fentanyl, have apparently short lasting effects when used as a single bolus. However, cessation of drug action in these settings is achieved by rapid redistribution of the drug to a large volume of distribution ( $V_d$ ), rather than by rapid drug metabolism or elimination. Repeated doses or prolonged infusions of such agents may saturate the  $V_d$ , and drug effects (which are now critically dependent on clearance rather than redistribution) may be significantly prolonged. The dependence of offset of drug effects on the duration of therapy has led to the concept of context-sensitive half time, which takes account of the cumulative effects of drugs with prolonged administration (figure 5). By this yardstick, the most desirable agents are those that have a short duration of action as a consequence of rapid excretion or metabolism (with no active metabo-

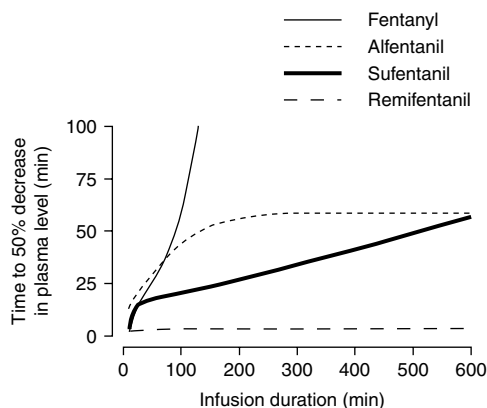
lites), and show little or no prolongation of their duration of effect with increases in duration of administration. Even short acting agents, such as propofol and alfentanil, may show some prolongation of effect with long-term use (figure 6). Perhaps the only current agent that seems substantially immune to this phenomenon is remifentanyl (figure 6; see section 5).

## 2.3 Pattern of Sedative Use

Many different sedatives have been used over the years in the NCCU. A survey of sedative use in the UK and Ireland in 1995 showed the frequency of use of different sedative and analgesic agents in neurointensive care units.<sup>[37]</sup> Most centres used a combination of a hypnotic and an opioid, the usual agents being propofol (65%), midazolam (80%), morphine (60%), fentanyl (46%), and alfentanil (26%). It is important to note that these figures predate the introduction of remifentanyl as an ICU sedative agent, and do not include the use of anaesthetic drugs as metabolic suppressants in the context of refractory intracranial hypertension. A repeat survey by the same authors in 2001<sup>[40]</sup> showed little change from this pattern, but data collection preceded recent concerns regarding problems with high dose propofol.



**Fig. 5.** Schematic diagram showing the context-sensitive half-times for thiopental sodium (thiopentone) and propofol. Note that the recovery characteristics of both drugs worsen with increasing duration of administration, but that this effect is much more prominent for thiopental sodium (reproduced from Shafer,<sup>[38]</sup> with permission from Elsevier Inc.).



**Fig. 6.** Schematic diagram showing the context-sensitive half-times for different opioids. Unlike the other agents, remifentanyl has constant recovery characteristics irrespective of duration of administration.<sup>[39]</sup>

None of these agents are ideal, and there are few published studies that compare sedative drugs either within or between the different pharmacological subclasses. The following discussion reviews the existing evidence for their use in head injury (see table II for a summary of the main classes of sedatives).

### 3. Benzodiazepines

Benzodiazepines (BZD) are non-specific CNS depressants that augment the action of GABA at GABA<sub>A</sub> receptors, causing increased conductance of chloride ions. Their clinical effects include anxiolysis, amnesia, and sedation, and they are also anticonvulsant. They remain the most frequently used sedatives on the NCCU, although their use appears to be on the decline in favour of propofol. Midazolam is the most commonly used BZD in the UK,<sup>[37]</sup> although diazepam has been used in the past and lorazepam is commonly used in the US.<sup>[41]</sup>

#### 3.1 Pharmacokinetics

The principal difference between the BZDs that is important in their use on the NCCU is their differing pharmacokinetic profiles. Diazepam has a prolonged elimination half-life of 20–40 hours, due to a combination of high lipid solubility and low hepatic clearance.<sup>[45]</sup> This compares unfavourably with the elimination half-lives of lorazepam (10–20 hours)<sup>[46]</sup> and midazolam (2–2.5 hours).<sup>[47]</sup>

Diazepam also has an active metabolite, desmethyldiazepam, with an elimination half-life of 93 hours, which adds to the prolonged sedation associated with the use of diazepam.<sup>[45]</sup> Lorazepam has a moderately long elimination half-life. It is metabolised in the liver to inactive metabolites, but may accumulate with repeated administration due to its long elimination half-life.<sup>[46]</sup> In a comparative study in critically ill surgery trauma patients, lorazepam was cost effective when compared with propofol or midazolam, but its use was more frequently associated with oversedation.<sup>[48]</sup>

Midazolam is also highly lipid soluble at physiological pH due to the closure of its imidazole ring, although at low pH it is water soluble. This causes a rapid onset of action. It is rapidly metabolised by the liver to a mixture of active ( $\alpha$ -hydroxymidazolam = 63% of midazolam potency,  $\alpha$ -hydroxymidazolam glucuronide = 9% of midazolam potency) and inactive (4-hydroxymidazolam) metabolites, accounting for its rapid offset of action.<sup>[47]</sup> This may make midazolam the more desirable BZD in terms of ease of titration,<sup>[48]</sup> with more predictable wake-up times in head-injured patients. However, accumulation of active metabolites may result in significant sedation,<sup>[49]</sup> and the pharmacokinetics of midazolam may be altered by different disease and physiological states and the use of concurrent medications. The metabolism of midazolam in critically ill patients may be impaired,<sup>[50]</sup> and multiple doses or prolonged infusions may cause drug accumulation and prolonged sedative effects after cessation of midazolam administration.<sup>[51]</sup> The elimination half-life of midazolam is increased in elderly patients, following surgery,<sup>[52,53]</sup> and in patients with severe liver disease.<sup>[50]</sup> While lorazepam has a longer half-life than midazolam (8–15 vs 3–11 hours) in healthy subjects, its clearance may be increased following neurotrauma<sup>[54]</sup> but its pharmacokinetics seem relatively unaltered by critical illness or organ failure.<sup>[54,55]</sup> Therefore, the more predictable pharmacokinetics of lorazepam represent a considerable advantage in sedating critically ill patients with multiorgan failure.<sup>[2]</sup>

#### 3.2 Cerebral Effects

BZDs all increase the seizure threshold and may be used as anticonvulsants.<sup>[56,57]</sup> Lorazepam, in par-



**Table II.** Summary of the main sedative agents used in the treatment of head-injured patients in the neurointensive care unit<sup>[41]</sup>

Drug	t <sub>1/2</sub> (h)	Drug metabolite accumulation	CBF	CMRO <sub>2</sub>	ICP	MAP	Seizure threshold	Other effects
Midazolam	2–2.5	+	↓	↓	(↓)	↓	↑	Interaction with peripheral benzodiazepine leucocyte receptors (clinical relevance?)
Lorazepam	0–20	++	↓	↓	(↓)	↓	↑	
Diazepam	20–40	+++	↓	↓	(↓)	↓	↑	
Morphine	1.7–4.5	++	(↓) <sup>a</sup>	(↓) <sup>a</sup>	(↑) <sup>a,b</sup>	(↓) <sup>a</sup>	(↓) <sup>c</sup>	Reduces reticuloendothelial cell function, macrophage migration and microbial killing <i>in vitro</i> (clinical relevance?). Remifentanyl pharmacokinetics unique, with excellent titrability and wake-up characteristics
Fentanyl	3.7	+	(↓) <sup>a</sup>	(↓) <sup>a</sup>	(↑) <sup>a,b</sup>	(↓) <sup>a</sup>	(↓) <sup>c</sup>	
Alfentanil	1.5	+	(↓) <sup>a</sup>	(↓) <sup>a</sup>	(↑) <sup>a,b</sup>	(↓) <sup>a</sup>	(↓) <sup>c</sup>	
Remifentanyl	0.15	–	(↓) <sup>a</sup>	(↓) <sup>a</sup>	(↑) <sup>a,b</sup>	(↓) <sup>a</sup>	(↓) <sup>c</sup>	
Thiopental sodium (thiopentone)	11.5	+++	↓	↓	↓	↓	↑	Marrow suppression and leucocyte respiratory burst suppression with high doses
Pentobarbital (pentobarbitone)	11.7–19.5	++	↓	↓	↓	↓	↑	
Methohexital (methohexitone)	4	–	↓	↓	↓	↓	↑	
Propofol	7.2	— <sup>d</sup>	↓	↓	↓	↓	↑	Lipid load, propofol infusion syndrome. Antioxidant (clinical relevance?). No adrenal suppression
Ketamine	2.6	+	↑	↑	↑	↑ <sup>e</sup>	↓	NMDA antagonist (clinical relevance?)
Etomidate	4.8	–	↓	↓	↓	↓	↑	Adrenal suppression, renal failure with propylene glycol (vehicle for infusion)

*Continued next page*

Table II. Contd

Drug	t <sub>1/2</sub> (h)	Drug metabolite accumulation	CBF	CMRO <sub>2</sub>	ICP	MAP	Seizure threshold	Other effects
Haloperidol	(24) <sup>f</sup>	-	→			→	↑	Extrapyramidal effects
Dexmedetomidine	2	-	→	↔	→	→	?	
Clonidine	20	-	→	↔	→	→	?	Part of Lund protocol

- a While opioids and benzodiazepines reduce CBF and CMRO<sub>2</sub>, there is a ceiling to these effects and they do not produce burst-suppression or an isoelectric EEG.
- b Rapid infusions or large doses of potent opioids may reduce MAP and CPP, and the resulting autoregulation-induced cerebral vasodilatation may increase CBV and ICP.
- c Several studies suggest that high dose opioids may increase epileptiform activity.<sup>[42-44]</sup> See text for discussion.
- d Consider context-sensitive half-time.
- e High doses of ketamine may result in MAP drops, especially in hypovolaemic patients, but MAP is generally elevated or maintained.
- f Figure shows duration of maximum.

**CBF** = cerebral blood flow; **CBV** = cerebral blood volume; **CMRO<sub>2</sub>** = cerebral metabolic rate; **CPP** = cerebral perfusion pressure; **EEG** = electroencephalogram; **ICP** = intracranial pressure; **MAP** = mean arterial pressure; **NDMA** = N-methyl-D-aspartate; t<sub>1/2</sub> = elimination half-life; ↓ = decrease; ↑ = increase; ↔ = no change; ? = inadequate data.

ticular, has a role in the treatment of epilepsy.<sup>[57]</sup> Midazolam causes a number of electroencephalogram (EEG) changes, including a decrease in alpha activity, an increase in theta-delta activity, low-voltage beta activity and high-frequency beta activity.<sup>[58,59]</sup> Animal studies have shown that BZDs improve neurological outcome following ischaemic brain injury<sup>[60]</sup> and have a protective effect against cerebral hypoxia following convulsions.<sup>[61]</sup> There are no reports of such effects in humans.

Benzodiazepines reduce CBF and CMRO<sub>2</sub> but there is a ceiling effect above which there is no additional effect on CMRO<sub>2</sub> (see figure 4),<sup>[9]</sup> and burst suppression or an isoelectric EEG cannot be achieved.<sup>[62]</sup> A study of head-injured patients showed a decrease in CBF and CMRO<sub>2</sub> during the administration of diazepam,<sup>[63]</sup> and CPP was unaffected. No associated decrease in ICP has been reported with diazepam therapy.<sup>[64]</sup> Similarly, midazolam decreased CBF and CMRO<sub>2</sub> in animals<sup>[62,65]</sup> and healthy volunteers,<sup>[66]</sup> although a study in patients undergoing craniotomy demonstrated no change in these indices.<sup>[67]</sup> ICP was not altered in patients with severe head injury who were treated with midazolam.<sup>[68]</sup> There was a significant decrease in CPP but this was due to a concomitant reduction in MAP.

Tolerance to the sedative effects of BZD occurs after only a few hours of treatment, leading to reduced efficacy and escalating doses,<sup>[69,70]</sup> or the requirement for the use of alternative drugs. A further adverse effect that has been reported during discontinuation of longer-term BZD therapy is a withdrawal syndrome,<sup>[71]</sup> manifested by tremors, seizures, hypertension and insomnia.

3.3 Extracerebral Effects

In the cardiovascular system, BZDs reduce systemic vascular resistance.<sup>[72]</sup> The reported effect on MAP is also variable, with midazolam causing no reduction in MAP in adult intensive care and normotensive neurosurgical patients,<sup>[64,73]</sup> a slight reduction in previously hypertensive neurosurgical patients<sup>[64]</sup> and a significant reduction in severely head-injured patients.<sup>[68]</sup> This latter study is the only one in which head-injured patients were studied. Although only 12 patients were included in the study, the results suggested that midazolam boluses should be used with extreme caution in head-injured

patients, especially when CPP is already critical. Several of the authors suggested that the haemodynamic effects of BZDs may become more significant in hypovolaemic patients. There is controversy as to whether BZDs preserve normal cardiovascular homeostatic reflexes.<sup>[74,75]</sup> BZDs are potent inhibitors of respiration by a central action and inhibit the cough reflex, effects that may become important when weaning patients off mechanical ventilation.

### 3.4 Flumazenil

This is an imidazodiazepine that is a specific benzodiazepine antagonist. Its use to reverse BZD sedation is not to be recommended in head-injured patients since it has been shown to increase ICP and decrease CPP in this situation.<sup>[76]</sup> It can also cause tachycardia, hypertension and seizures when used to reverse BZD sedation.<sup>[77]</sup>

### 3.5 Summary

Midazolam, by virtue of its shorter half-life and more rapid onset and offset of action, is the arguably the most appropriate BZD for use in the NCCU. It reliably reduces CMRO<sub>2</sub> and CBF, but with no associated decrease in ICP. It has the advantage of reducing the seizure threshold, but cannot induce burst suppression. It may cause significant systemic hypotension, with a detrimental effect on the CPP. Care must still be taken to avoid accumulation in prolonged use, especially in liver disease and in elderly patients. Midazolam has an established role in the NCCU, either for maintenance of sedation, or as an adjunct to other sedatives. However, its potential to accumulate (especially in severely ill patients) and to cause hypotension, and its inability to reliably reduce ICP mean that it is not an ideal agent. Lorazepam may be a useful and inexpensive agent for patients who require prolonged sedation but do not require rapid reversal of sedation for neurological evaluation. An additional advantage is its predictable pharmacokinetic behaviour, even in the setting of multiorgan failure.

## 4. Propofol

Propofol is a phenol derivative that has high lipid solubility but is almost insoluble in water. It is formulated as an emulsion in a combination of soya

bean oil, glycerol and egg phosphatide, and it is this, rather than the drug itself, that is responsible for some of its adverse effects, as outlined below. Since the introduction of propofol in 1986, it has gained widespread use as an induction agent and is now commonly used as a sedative agent on intensive care units, including the NCCU,<sup>[37,40]</sup> where it is given as an infusion with additional boluses as required. It is presented as a 1% or 2% solution. It has a rapid onset of action, is rapidly cleared from the plasma, and is metabolised by the liver to quinol and propofol glucuronides and 4-quinol sulphate, which are inactive. Propofol has an elimination half-life of 3–4.8 hours. After even prolonged infusions, recovery of consciousness following its cessation is reliable, reported as 15 minutes after an infusion lasting several days.<sup>[78]</sup> Despite these reports, it must be recognised that the kinetics of the drug at the effect site (where the drug exercises its pharmacodynamic effects) can substantially vary with the duration of treatment – i.e. the half-time for the clinical effects of propofol are context-sensitive (figure 5).<sup>[79]</sup> These effects have been carefully considered in the design of dosage regimens for total intravenous anaesthesia (TIVA),<sup>[80]</sup> but are rarely considered during use in critical care sedation, even with other agents.<sup>[81]</sup> There are several difficulties in extending TIVA protocols to sedation in critical care, including altered pharmacokinetics in critically ill patients, pharmacokinetic interactions with other drugs, and the effects of non-drug therapy. For example, there is concern that hypothermia<sup>[82]</sup> and catecholamines<sup>[83]</sup> (both of which are commonly used in head injury) may alter propofol metabolism. Also of some concern are reports of the development of both pharmacokinetic and pharmacodynamic tolerance<sup>[84]</sup> to propofol during prolonged use. These issues probably need more attention when propofol is administered for long periods of sedation in high doses in critically ill patients.

### 4.1 Cerebral Effects

Propofol reduces CBF, CMRO<sub>2</sub> and ICP reliably in a number of studies but this is often compounded by a reduction in CPP, usually as a result of a lowering of the MAP. Ten patients with closed head injury were given an infusion of propofol (150 µg/kg/min) during an operation for orthopaedic inju-

ries.<sup>[85]</sup> There were significant reductions in CPP, regional CBF and ICP in all patients during the propofol infusion, which returned to baseline when propofol was stopped. An infusion of propofol (mean rate 2.88 mg/kg/h) was administered to 10 patients with severe head injury in intensive care, causing a significant reduction in ICP, significant only at 2 hours, and an increased CPP, significant only at 24 hours.<sup>[86]</sup> In a larger study, 42 patients with severe head injury received either a combination of morphine and a propofol infusion (propofol  $55 \pm 42$  µg/kg/min and morphine  $1.3 \pm 0.7$  mg/h) or morphine alone ( $10 \pm 6.7$  mg/h).<sup>[87]</sup> The propofol group required less neuromuscular blocking agents, BZDs, barbiturates and CSF drainage ( $p < 0.05$ ), and had a lower ICP, but the latter difference was only significant at 3 days post-injury. A further study in 15 severely head-injured patients who received either an infusion of propofol (mean rate 232 mg/h) or morphine (mean rate 2.3 mg/h) and midazolam (mean rate 2.8 mg/h) showed a reduction in global brain metabolism in the propofol group but no difference in MAP, ICP or CPP.<sup>[88]</sup> A bolus of propofol (2 mg/kg over 90 seconds) produced a significant reduction in ICP and CPP in six severely head-injured patients.<sup>[89]</sup>

Many authors have compared propofol with midazolam for sedation in critically ill patients.<sup>[90-92]</sup> Propofol is reported to be as safe as midazolam in terms of adverse effects, and may be associated with a shorter wake-up time<sup>[90]</sup> and a better quality of sedation<sup>[91]</sup> than midazolam.

Propofol has been used successfully to treat status epilepticus,<sup>[93-96]</sup> and one study confirmed successful treatment of status epilepticus with EEG recordings.<sup>[96]</sup> This is despite initial reports of induction-related epileptiform movements following its introduction,<sup>[97]</sup> and other reports of grand mal seizures associated with propofol therapy.<sup>[98,99]</sup> Myoclonic activity has been reported following propofol induction,<sup>[100]</sup> which may be confused with epileptic activity. Propofol is also effective in achieving burst suppression.<sup>[101]</sup> Animal studies suggest a large reduction in CBF (38–58%) and CMRO<sub>2</sub> (22–43%) at doses that produce burst suppression,<sup>[102-104]</sup> but usually at the expense of a fall in MAP (see later). Propofol may have neuroprotective effects other than those attributable to cerebral

metabolic suppression,<sup>[105]</sup> but this finding has not been confirmed in other studies.

## 4.2 Extracerebral Effects

Propofol, either by infusion or bolus is reported to cause a reduction in MAP or an increased inotropic requirement in many studies of head-injured patients,<sup>[85-87,89]</sup> and neurosurgical patients,<sup>[101,102,106,107]</sup> although one study reported no effect on MAP. At a dosage required to achieve burst suppression in neurosurgical patients (100–200 µg/kg/min), one paper demonstrated significant decreases in heart rate (19%), MAP (20%), cardiac index (23%) and left ventricular stroke work index (26%), which were attributed to venodilation and cardiac depression at this dosage.<sup>[101]</sup>

## 4.3 Adverse Effects Attributable to the Carrier

As mentioned earlier, the formulation of propofol may be responsible for a number of adverse effects. The lipid component can cause hypertriglyceridaemia, especially in large doses over long time periods,<sup>[108]</sup> an effect that could be reduced with the use of the 2% solution. It also has a significant calorific content, providing 1.1 kcal/mL, which should be taken into account during nutritional assessments. Anaphylactoid reactions following propofol usage have also been attributed to the carrier.<sup>[109,110]</sup>

Propofol administration has been associated with an elevation in pancreatic enzyme levels<sup>[111]</sup> and frank pancreatitis.<sup>[112,113]</sup> In one study, 40 surgical patients were randomly assigned to receive either anaesthesia with propofol (2.5 mg/kg bolus followed by maintenance of 4–10 mg/kg/h), or thiopental sodium induction (5–7 mg/kg) followed by maintenance with 0.5% isoflurane.<sup>[114]</sup> Both groups received 50% nitrous oxide in oxygen. The two groups showed no differences in plasma cholesterol, triglyceride, amylase or lipase levels postoperatively. However, this was a short-term study, and may not reflect the biochemical changes occurring after prolonged use of propofol, e.g. as in the NCCU. A further potential adverse effect of the carrier is infection,<sup>[115,116]</sup> and some authors suggest that propofol infusions are changed every 6 hours. A more

recent formulation of propofol that contains edetic acid (EDTA)<sup>[117]</sup> reduced the risk of infection without any significant change in sedative profile or trace element metabolism.<sup>[118,119]</sup> Initial reports that this formulation of propofol was associated with an improved outcome compared with the standard preparation<sup>[120]</sup> require confirmation in further studies.

#### 4.4 The 'Propofol Infusion Syndrome'

Prolonged propofol administration has been associated with a 'propofol infusion syndrome', which was first reported in critically ill paediatric patients<sup>[121,122]</sup> and is of uncertain aetiology. The syndrome comprises metabolic acidosis, lipaemic serum, hepatomegaly, rhabdomyolysis and cardiac failure. A review of the reported cases of propofol infusion syndrome in children published in 1995<sup>[123]</sup> found that factors associated with development of the syndrome included:

1. Prolonged propofol infusion of more than 48 hours duration.
2. Dosage of propofol greater than 4 mg/kg/h.
3. Age: 13 of the 18 case reports reviewed involved children aged 4 years or younger.
4. Respiratory tract infections: present in the majority of children who developed the syndrome.

Propofol infusion syndrome has been specifically reported in the NCCU setting in a case report of a 13-year old girl with closed head injury,<sup>[124]</sup> and in adults with head injury.<sup>[125]</sup> In the latter study, a retrospective cohort analysis of head-injured patients reported seven patients whom the authors judged to have died from the propofol infusion syndrome out of 67 patients at risk. Increased mortality was associated with high dosage, and long-term propofol infusion. The risk of developing the syndrome showed an odds ratio of 1.93 (95% CI 1.12–3.32,  $p = 0.018$ ) for every mg/kg/h increase in mean propofol dose above 5 mg/kg/h. Patients exhibited refractory tachyarrhythmias, although left ventricular dysfunction was not always present. Rhabdomyolysis, hyperkalaemia and prolonged or terminal acidosis were observed, but hyperlipidaemia was not a feature. The median onset of the syndrome was 67 hours after starting high dose propofol, and the median time to death was 91

hours. While it is clearly important to avoid high dose propofol, it has been questioned whether the patients actually died of a specific cardiac effect of propofol, or this simply represented cardiac depression and changes in electrolyte homeostasis that might be observed with high doses of many anaesthetic agents,<sup>[126,127]</sup> including barbiturates.<sup>[128]</sup>

It has been suggested that head-injured patients are at particular risk of the propofol infusion syndrome because of the prolonged need for anaesthetic doses of propofol to act as a metabolic depressant, and the possible contribution to metabolic acidosis and cardiac failure of the frequent use of vasopressors.<sup>[125]</sup> The actual mechanism of propofol infusion syndrome is the cause of some debate. It is unclear whether it is the drug itself, its metabolites, the lipid emulsion, or a combination of these factors that is responsible. Recent evidence has implicated abnormalities in acylcarnitine handling.<sup>[129]</sup> It is notable that major cardiovascular instability has also been reported with burst-suppression doses of thiopental sodium and has been attributed to its effects on  $\text{Na}^+$ / $\text{K}^+$  channels.<sup>[128]</sup>

In addition to these extracerebral effects on the cardiovascular system, which might be expected in a potent intravenous anaesthetic, propofol has also been reported to have other properties that may be of therapeutic relevance.<sup>[130]</sup> Perhaps the most prominent of these is a significant antioxidant capacity, which may protect against oxidant-mediated haemolysis, provide cytoprotection in hepatic ischaemia reperfusion injury, and contribute to the neuroprotective effects of the agent.

#### 4.5 Summary

Propofol, unlike the other sedatives discussed (with the exception of remifentanyl), is unique in its rapid clearance and reliable offset of action, even after long-term infusions. Other advantages include a reliable reduction in  $\text{CMRO}_2$ , CBF and ICP, factors that have increased its use in head-injured patients. It is useful both as a continuous infusion to provide sedation, and also as rescue treatment during episodes of increased ICP. Disadvantages include the reduction in MAP during infusion and bolus therapy, and the many adverse effects associated with the emulsion in which propofol is formulated. In the absence of alternatives, propofol will,

**Table III.** Opioid receptor subtypes

Receptor	Effects	Opioid receptor effects
$\mu_1$	Supraspinal analgesia	Morphine, fentanyl, alfentanil, remifentanil and sufentanil +++; codeine +
$\mu_2$	Ventilatory depression, bradycardia, physical addiction	Morphine, fentanyl, alfentanil, remifentanil and sufentanil +++; codeine +
$\kappa$	Sedation, spinal analgesia	Morphine ++, sufentanil +
$\Sigma$	Dysphoria, hallucinations, respiratory stimulation	
$\Delta$	Analgesia, behavioural effects, epileptogenic	Morphine, fentanyl, alfentanil, remifentanil, sufentanil and codeine +

+ = minimal effect; ++ = moderate effect; +++ = marked effect.

however, remain a well-used drug in the treatment of head-injured patients.

## 5. Opioids

Opioids are an intrinsic part of the sedative regimen for most head-injured patients. Not only do they provide analgesia and improved tolerance of mechanical ventilation and other therapeutic interventions, but they add to the sedation provided by other sedative agents, and are thus included in this review. In the UK, the most frequently used opioids are morphine (60% of NCCUs using this routinely), fentanyl (46%), alfentanil (26%) and codeine (20%).<sup>[37]</sup> Sufentanil has also been widely reported in the literature. Remifentanil is a new opioid currently undergoing clinical trials. Its particular attraction for use in the NCCU is that it has an ester linkage that is rapidly hydrolysed by plasma esterases to an inactive metabolite, and therefore has a rapid and reliable offset of action and does not accumulate.<sup>[131]</sup>

Four subclasses of opioid receptors have been identified:  $\mu$ ,  $\kappa$ ,  $\delta$  and  $\sigma$ .<sup>[132]</sup> They are found widely in the CNS and peripherally.  $\mu$  Receptors are further sub-classified into  $\mu_1$  and  $\mu_2$  receptors.<sup>[133]</sup> Table III summarises the effects of stimulation of the different opioid receptors and the differential actions of opioid agonists at these receptors.

As with the BZDs, the main differences between the opioids lie in their pharmacokinetics (figure 6). Morphine has a low lipid solubility and slow CNS penetration, so its onset of action is relatively slow. It has a half-life of 2–3 hours,<sup>[134]</sup> but this is increased in renal failure as about 10% of the parent drug is excreted unchanged in the urine.<sup>[135]</sup> In addition, morphine is metabolised in the liver to

morphine-3-glucuronide and morphine-6-glucuronide, the latter of which has a potency several times that of morphine, and accumulates in renal failure.<sup>[42]</sup> By contrast, fentanyl, alfentanil and sufentanil are highly lipid soluble, so have a fast onset of action. Alfentanil, by virtue of its shorter half-life, is less likely to accumulate than fentanyl when given by infusion. They are metabolised by the liver to inactive metabolites,<sup>[43]</sup> so renal impairment does not prolong their action but metabolism is delayed in various disease states. Cardiac failure reduces the clearance of fentanyl.<sup>[44]</sup> Critical illness<sup>[136]</sup> and cirrhosis,<sup>[137]</sup> respectively, reduce the clearance and increase the half-life of alfentanil.

The recent introduction of remifentanil into ICU practice represents a substantial advance in the management of sedation in patients with head injury. Remifentanil is broken down by nonspecific plasma and tissue esterases.<sup>[131]</sup> Its rapid onset and offset, ease of titration, and stable pharmacokinetics could potentially make it an ideal agent in this group of patients. In particular, it has a constant context-sensitive plasma half-life, and its duration of offset is largely uninfluenced by the duration of therapy or dosage used.<sup>[138]</sup> While formal evaluation of its use in ICU sedation for head injury is limited, its effect on CNS and cerebrovascular physiology have been well studied in neuroanaesthesia.<sup>[139–143]</sup> The pharmacodynamics of remifentanil seem similar to those of other opioid agents, with expected cerebrovascular effects. Warner et al. showed that remifentanil and alfentanil had similar effects on systemic haemodynamics, but no effect on ICP in patients undergoing craniotomy.<sup>[140]</sup> Remifentanil and fentanyl have similar effects on baseline cerebral blood flow and CBF carbon dioxide reactivity,<sup>[144]</sup> and

magnetic resonance techniques suggest that the agent has no adverse effects on measures of cerebral compliance in healthy volunteers.<sup>[145]</sup>

The real benefit of this agent would be expected to relate to its pharmacodynamics, and the agent has been widely evaluated in general intensive care settings.<sup>[146-151]</sup> Early publications suggest that remifentanyl is likely to be a useful agent in neurotrauma,<sup>[152]</sup> and a preliminary report suggested that its pharmacokinetic properties may be beneficial in this setting.<sup>[153]</sup> Karabinis et al.<sup>[153]</sup> studied the time taken to allow neurological evaluation after down-titration of sedative agent in patients with neurotrauma receiving remifentanyl, fentanyl and morphine, and found that remifentanyl showed a substantially less increase in offset time with prolonged therapy compared with the other two agents. This limited experience in neurotrauma is consistent with experience in other critically ill patient populations. In particular, remifentanyl showed little accumulation even in patients with severe renal failure, and levels of its main metabolite, remifentanyl acid, did not reach levels that were clinically significant.<sup>[154]</sup> While reductions in body temperature reduced remifentanyl clearance by 3% per 1°C,<sup>[155]</sup> these effects are unlikely to be clinically significant in neurotrauma patients who are treated with moderate hypothermia.

### 5.1 Cerebral Effects

Opioids have the advantage of having minimal effect on CBF and CMRO<sub>2</sub>.<sup>[156,157]</sup> However, their effects on ICP and CPP seem to be less favourable. Many authors have reported an increase in ICP during opioid therapy in head-injured patients.<sup>[158-162]</sup> Thirty patients with severe head injury who were given a bolus of morphine (0.2 mg/kg) or fentanyl (2 µg/kg) had an increase in ICP, decrease in MAP and consequent reduction in CPP.<sup>[158]</sup> CBF in these patients was reported as unchanged and carbon dioxide reactivity as preserved, but autoregulation in response to a hypertensive challenge was impaired or abolished in 56.7% of patients. Similar changes in ICP and MAP were reported following boluses of sufentanil or fentanyl in another study of patients with severe head injury.<sup>[162]</sup> A further study reported the effects of boluses and subsequent infusions of sufentanil, fentanyl and alfentanil in 10

head trauma patients.<sup>[159]</sup> Administration of all drugs was associated with a significant increase in the ICP, although the effect was transient, peaking at between 3 and 5 minutes, and returned to baseline at 15 minutes. These rises in ICP are associated with reductions in MAP and CPP in all cases and are thought to be mediated by autoregulatory vasodilatation and increases in CBV. Indeed, even a large bolus dose of sufentanil (3 mg/kg) had no effects on ICP if MAP was maintained using vasopressors, although ICP elevations were observed if MAP was not maintained.<sup>[160]</sup>

There have been a number of case reports of epileptiform activity following opioid therapy during anaesthesia,<sup>[163-165]</sup> but it is unclear whether this reflects true seizure activity. In high doses, all opioids can cause seizures, but an EEG recording during one episode of epileptiform activity in humans showed no seizure activity.<sup>[166]</sup>

### 5.2 Extracerebral Effects

Opioids produce hypotension by reducing sympathetic tone and increasing parasympathetic tone,<sup>[167]</sup> but they have no effect on cardiac contractility.<sup>[168]</sup> All opioids can cause a vagally-mediated bradycardia,<sup>[169]</sup> although this is less common with infusions than rapid injections.

A further mechanism for opioid-associated hypotension is histamine release. There are many reports of histamine release following opioid therapy,<sup>[170-173]</sup> with associated haemodynamic changes, including hypotension and tachycardia. The mechanism appears to be a direct action of the opioids on histamine-containing cells rather than an allergic-type response, and the action appears to be restricted to morphine-like drugs; synthetic opioids such as fentanyl and sufentanil are free of this adverse effect.<sup>[170]</sup> The hypotension produced is of particular importance in head-injured patients, where maintenance of CPP is of paramount importance in preventing secondary neuronal injury.

Opioids cause profound respiratory depression and suppression of the cough reflex. These may be helpful in ventilated patients, but are a disadvantage in the weaning phase of NCCU care. As discussed previously, the effects of morphine may be prolonged, especially in renal impairment, but fentanyl

is also associated with a delayed 'rebound' effect that can be delayed for up to 4 hours after stopping an infusion. This is thought to be due to enterohepatic circulation or mobilisation of sequestered stores. Opioids can also cause muscle rigidity,<sup>[174]</sup> an effect that can affect the respiratory muscles and interfere with ventilation.

Gastrointestinal effects of opioids include nausea and vomiting, although this is not an important problem in unconscious patients. However, reduced gastrointestinal motility is a concern in sedated and awake subjects, and leads to delayed gastric emptying,<sup>[175,176]</sup> intolerance of nasogastric feeding, and constipation. These effects of opioid drugs add to the altered gastrointestinal motility that occurs as a direct consequence of head injury (see section 1.2).

Less well documented potential adverse effects of opioids include suppression of the immune response,<sup>[130]</sup> a factor that may contribute to hospital-acquired infections in the NCCU. Initial fears that high-dose opioids may be directly neurotoxic have not been justified.<sup>[177,178]</sup>

### 5.3 Summary

Despite many potential disadvantages for the use of opioids in the NCCU, these agents remain in widespread use. In practice, the potential adverse effects of these agents can be minimised with care, and they are extremely useful because of their ability to complement sedation, improve tolerance of mechanical ventilation and to provide effective analgesia. Opioids are frequently used in combination with hypnotic agents such as benzodiazepines and propofol, and can reduce sedation requirements with improved haemodynamic consequences. Boluses of opioids have been reliably shown to cause hypotension and rises in ICP, so care should be taken when administering opioids in this way to patients with a critical CPP.

There is little to choose between the frequently used opioids in terms of detrimental effects (increases in ICP and decreases in MAP and CPP with bolus administration), but the shorter acting drugs have advantages in terms of a shorter duration of action and a reduced tendency to accumulate. The availability of remifentanyl as an ICU agent (now approved in the US and the UK) provides a sedative

agent with unique pharmacokinetic characteristics that enable easy titration and rapid emergence. Clinical experience with remifentanyl in this setting is still relatively limited, but it appears likely that this agent will play a major role in sedation in head injury. While longer acting opioids can be effectively antagonised by naloxone, a specific  $\mu$ -receptor antagonist, this does not provide a risk-free alternative. Naloxone reversal does have the potential to allow rapid neurological assessment during opioid therapy, although rapid reversal of opioid narcosis can be associated with adverse effects, such as hypertension and myocardial ischaemia, and rises in ICP. While these adverse effects would also be observed with the rapid offset of opioid effects with remifentanyl cessation, the presence of naloxone could make re-sedation more difficult and limit ability to titrate.

## 6. Barbiturates

Barbiturates, particularly pentobarbital (pentobarbitone), have been extensively studied in head injury. In the UK, thiopental sodium is the most commonly administered barbiturate, used in 56% of NCCUs.<sup>[179]</sup> Barbiturates exert their effects by stimulating GABA receptors<sup>[180]</sup> and inhibiting excitatory  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors in the CNS to produce dose-dependent sedation and general anaesthesia. Barbiturates are very lipid soluble, allowing rapid diffusion into the CNS and rapid onset of action. Thiopental sodium is predominantly metabolised in the liver, although a small amount is excreted unchanged by the kidneys. It has a long elimination half-life of 11.6 hours in surgical patients and is metabolised by zero-order kinetics at the higher plasma levels that result from prolonged infusions and high dosages.<sup>[181]</sup> These figures are broadly in agreement with data obtained from longer infusion periods in critically ill adults and children with neurotrauma.<sup>[182-185]</sup> This causes an accumulation of thiopental sodium, especially after repeated doses or prolonged infusions, which are often employed to achieve burst suppression in refractory intracranial hypertension. Drug level measurement suggests that the elimination of thiopentone shifts from first- to zero-order kinetics when plasma concentrations exceed 30 mg/L, and plasma levels >40



mg/L are required to produce burst suppression.<sup>[185]</sup> It is therefore important to identify the dosage of thiopental sodium that provides the maximal degree of cerebral metabolic suppression, since a higher dosage results in no additional CNS effects and produces increasing and dangerous cardiovascular depression with a greater prolongation of emergence times. This is particularly detrimental in the NCCU, where rapid offset of action is desirable to assess neurological status.

Ideally, barbiturate dosage requirements are defined using EEG monitoring, in order to achieve a burst-suppressed EEG, in which periods of isoelectricity (suppression) are interspersed with bursts of electrical activity, with the former typically representing greater than 50% of the trace. However some guidance is also available from the literature. Following a loading dose (typically 40 mg/kg),<sup>[186]</sup> infusion rates of 4–8 mg/kg/h are usually required to maintain burst-suppression patterns on EEG. More recent data<sup>[185]</sup> suggest that the lower end of this dose range may be more appropriate in most patients who require long-term thiopentone in the ICU setting. Measurement of plasma drug levels may provide useful guidance during the recovery periods following thiopental coma,<sup>[187]</sup> with recovery of pupillary function at plasma levels of 50 mg/L and motor responsiveness at 12 mg/L.

Pentobarbital also has a long half-life, measured as  $15.6 \pm 3.9$  hours in head-injured patients.<sup>[188]</sup> Methohexital (methohexitone) is unusual in having a shorter half-life of 4 hours, and has been shown to have a more rapid elimination than thiopental sodium after prolonged infusion.<sup>[189]</sup> However, methohexital has not been widely studied in head injury, so further discussion of the barbiturates will include only pentobarbital and thiopental sodium.

## 6.1 Cerebral Effects

Barbiturates have long been known to reduce ICP and CBF<sup>[190]</sup> and have been shown to reduce ICP that is refractory to other medical and surgical interventions.<sup>[191]</sup> This may be due to a combination of suppression of brain metabolism<sup>[192]</sup> and altered cerebral vascular tone.<sup>[193]</sup> EEG effects include an increase in fast beta activity at low concentrations and burst suppression at higher doses.

Evidence for the use of barbiturates in head injury falls into two categories that will be discussed next.

### 6.1.1 Treatment of Elevated Intracranial Pressure (ICP)

Several studies have linked the administration of barbiturates with outcome. The administration of barbiturates in severe head injury was associated with improved ICP control and an improved outcome in one study.<sup>[194]</sup> These results were echoed by a second study in 60 patients.<sup>[195]</sup> There was improved control of elevated ICP in the group receiving pentobarbital in a further study of 73 severely head-injured patients.<sup>[196]</sup> However, this translated into a survival advantage only in a subgroup of patients who had no preceding cardiac complications. Despite this, a recent meta-analysis<sup>[197]</sup> of the use of barbiturates in head injury found no evidence that barbiturate therapy in head injury improves outcome. However, the conclusions of this meta-analysis are in conflict with expert recommendations provided in internationally accepted guidelines.<sup>[1]</sup>

A study investigating a link between cerebral vasoreactivity and ICP showed that in patients in whom there was an intact CBF response to hyperventilation, barbiturate therapy was associated with a decrease in CBF, CMRO<sub>2</sub> and ICP.<sup>[198]</sup> These responses were absent in patients in whom cerebral vascular reactivity to hyperventilation was reduced or abolished. In another study of head-injured patients, pentobarbital was compared with mannitol for initial treatment of raised ICP, with no difference in outcome.<sup>[199]</sup> Pentobarbital appeared to fare worse, with a significant reduction in the CPP, and, in a subgroup of patients with diffuse cerebral injury, those treated with pentobarbital had a mortality of 77% compared with that in the mannitol group of 41%.

### 6.1.2 Prophylaxis Against Raised ICP and Ischaemic Neuroprotection

In a study of 53 head-injured patients, subjects were randomised to receive conventional treatment plus or minus prophylactic pentobarbital.<sup>[200]</sup> Pentobarbital was started as soon as possible after head injury, at a dose sufficient to cause burst suppression. There were no differences between the groups

in terms of outcome, the incidence of elevated ICP, the duration of ICP elevation or the response of the ICP elevations to treatment, and the authors concluded that they could not recommend the administration of barbiturates in prophylaxis of raised ICP in head injury. Similarly, while there is substantial evidence of barbiturate neuroprotection in experimental focal ischaemia, these results have not translated into general clinical benefit,<sup>[201]</sup> despite isolated positive studies.<sup>[186]</sup>

## 6.2 Extracerebral Effects

Barbiturates are widely known to reduce MAP by a combination of myocardial and central vasomotor depression.<sup>[202,203]</sup> Studies of barbiturate use in head injury confirm this phenomenon.<sup>[196,197,199]</sup> They depress respiration and decrease smooth muscle tone, an effect that reduces tolerance of nasogastric feeding.<sup>[204]</sup> There is loss of thermoregulation in experimental models,<sup>[202]</sup> which is confirmed in some clinical studies.<sup>[197]</sup> Barbiturates also inhibit leucocyte phagocytosis and respiratory burst,<sup>[205]</sup> causing increased susceptibility to infection. High doses of barbiturates may suppress the bone marrow and reduce neutrophil production in sepsis.<sup>[206]</sup>

In addition to these well documented adverse effects, there is emerging concern regarding the occurrence of refractory cardiac dysrhythmias and cardiac failure with high dose barbiturates, particularly during emergence from coma.<sup>[128]</sup> This has often been associated with severe hyperkalaemia, and while attempts have been made to relate this to the documented effects of barbiturates at K<sup>+</sup> channels,<sup>[207]</sup> the mechanism of cardiovascular dysfunction in this setting remains unclear.

## 6.3 Summary

Barbiturates produce reliable reductions in CBF, control of ICP and suppression of epileptic foci. This is at some cost, however. In particular, the reduction in MAP may produce significant reductions in CPP, a factor that may worsen the outcome of head-injured patients. In addition, the undesirable pharmacokinetics means that the prolonged elimination and accumulation of barbiturates, especially after repeated doses, may delay neurological assessment. There are also emerging concerns regarding

the development of poorly explained cardiovascular failure in association with high dose barbiturate use. No causal association has been demonstrated, but caution is advisable. While barbiturates remain a valuable tool in the treatment of refractory intracranial hypertension and status epilepticus, they must be used with caution.

## 7. Ketamine

Ketamine is a phencyclidine derivative that acts as a non-competitive antagonist at the NMDA receptor, which is a subtype of EAA receptor within the CNS. It has a short elimination half-life of 2.6 hours, but some of its metabolites may have anaesthetic effects, particularly norketamine,<sup>[208]</sup> leading to potential accumulation with repeated doses. Ketamine has a number of advantages that would make it a useful drug in the NCCU. Its cardiovascular profile makes it useful when cardiovascular depression is best avoided. It is well known to cause an increase in systemic blood pressure and heart rate,<sup>[209-211]</sup> and is therefore useful in hypovolaemic or hypotensive patients.

The antagonism of NMDA receptors by ketamine may have a specific protective role in the treatment of head-injured patients. It antagonises excitatory amino acids at the NMDA receptor and may reduce the consequent calcium ion mobilisation and neuronal damage that occurs in head injury.<sup>[212]</sup> Ketamine has been shown to be neuroprotective in studies of ischaemic and traumatic head injury in rats.<sup>[212-215]</sup> In addition, cerebrovascular responsiveness to arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) is preserved<sup>[216]</sup> and burst suppression can be achieved.<sup>[217]</sup>

Despite the potential benefits of ketamine in head-injured patients, it has not gained widespread use because of reported detrimental effects on CBF, CMRO<sub>2</sub> and ICP. Studies have repeatedly reported increases in CMRO<sub>2</sub>, increases in CBF by 50–80% and consequent increase in ICP,<sup>[216,218-220]</sup> with recommendations not to use it in the NCCU. Some studies have been published, however, describing the use of ketamine in head injury. In one report, patients with severe head injury were given either ketamine and midazolam or fentanyl and midazolam.<sup>[209]</sup> The ketamine group had a lower requirement for catecholamines, a CPP that was on average

8mm Hg higher and an ICP that was 2mm Hg higher than the fentanyl group, and no difference in overall outcome. The authors suggested it is an appropriate therapy in head-injured patients. In another study, three different doses of ketamine, in addition to a propofol infusion, were administered to deepen sedation in eight artificially ventilated head-injured patients.<sup>[217]</sup> All three doses of ketamine were associated with a statistically significant decrease in ICP and no change in CPP, jugular bulb venous oxygen saturation and middle cerebral artery blood flow velocity. The authors concluded that ketamine may not cause adverse cerebral haemodynamics in head-injured patients sedated with propofol, and recommended larger studies.

A further disadvantage of ketamine therapy is its reduction of the seizure threshold, demonstrated by EEG changes,<sup>[221]</sup> an increase in epileptiform movements in epileptic patients<sup>[222]</sup> and an increased frequency of seizures in epileptic patients for months after receiving a ketamine anaesthetic.<sup>[223]</sup> Despite these reports, ketamine has been successfully used for control of status epilepticus.<sup>[224]</sup>

### 7.1 Summary

Ketamine is unusual among potential sedative agents in its maintenance of systemic blood pressure. However, it is not recommended for use in head injury because of the reported increase in CMRO<sub>2</sub>, CBF and ICP during its administration, and the possible lowering of the seizure threshold.

## 8. Etomidate

Etomidate is a carboxylated imidazole derivative, most commonly used as an intravenous induction agent in cardiovascular instability. It has a number of features that would make it useful on the NCCU. It is rapidly cleared, with an elimination half-life of 2.6 hours.<sup>[225]</sup> It reduces both CBF and ICP,<sup>[226-229]</sup> can achieve burst suppression,<sup>[230]</sup> causes minimal cardiovascular depression<sup>[231,232]</sup> and is non-cumulative.<sup>[233]</sup> Several studies have reported the efficacy of etomidate in head-injured patients.<sup>[229,234-236]</sup> Etomidate is reliably shown to reduce ICP and preserve CPP, with variable effects on MAP. Generally, MAP is preserved or only slightly reduced, however one group reported that boluses of etomidate

were associated with 'occasionally serious' episodes of hypotension that may be associated with hypovolaemia.<sup>[193]</sup> Consequent reductions in CPP were usually small at less than 10mm Hg.

Despite the many advantages of etomidate, its use in the NCCU is limited by associated adrenal suppression. Etomidate is a reversible inhibitor of the enzyme 11- $\beta$ -hydroxylase, which converts 11-deoxycortisol to cortisol.<sup>[237,238]</sup> The enzyme is also involved in the synthesis of aldosterone, causing decreased mineralocorticoid effect.<sup>[239]</sup> While a single dose of etomidate can reduce the synthesis of cortisol and aldosterone for up to 24 hours,<sup>[240]</sup> the clinical significance is unclear. Prolonged infusions of etomidate have been shown to cause a significant increase in mortality in the general ICU.<sup>[241]</sup> Although coincident use of corticosteroids may enable the safe use of etomidate, these problems have limited its use in the intensive care setting. An additional concern relates to the development of renal failure and other adverse effects when an etomidate preparation formulated in propylene glycol is used for long-term infusions.<sup>[242-246]</sup> This preparation is no longer marketed in the UK, but is available in other countries, including the US (Bedford Laboratories, Bedford, Ohio, USA).

### 8.1 Summary

Etomidate causes less cardiovascular instability than the other sedatives, except ketamine, and produces a reduction in CBF and ICP. It is not often used as a long-term sedative in many intensive care units because it causes adrenal suppression and an associated increase in mortality, although this is managed in some units with associated corticosteroid therapy. Formulations in propylene glycol may have adverse effects attributable to the solvent.

## 9. $\alpha_2$ -Adrenoceptor Agonists

These include clonidine and dexmedetomidine. They cause sedation, anxiolysis and amnesia by their action at central  $\alpha_2$ -adrenoceptors and also have the advantages of a lack of respiratory depression and a significant anaesthetic sparing effect.<sup>[247]</sup>

Dexmedetomidine is the newer agent, and has greater specificity for the  $\alpha_2$ -adrenoceptor than clonidine.<sup>[248]</sup> It has an elimination half-life of 2

hours<sup>[249]</sup> and is metabolised in the liver to methyl and glucuronide metabolites. Its clearance is reduced in liver failure, and it inhibits the CYP2D6 component of the enzyme cytochrome P450 (CYP).<sup>[250]</sup>

$\alpha_2$ -Adrenoceptors are found throughout the CNS,<sup>[251]</sup> and their direct stimulation by dexmedetomidine may be responsible for the reduction in CBF without a reduction in cerebral metabolism that has been demonstrated in animals.<sup>[252,253]</sup> Despite the altered CBF/CMRO<sub>2</sub> ratio, there is no evidence that global cerebral ischaemia occurs. Other animal work suggests that  $\alpha_2$ -agonists have a neuroprotective effect. They have been shown to improve neurological outcome following cerebral ischaemia.<sup>[254]</sup> The only study of dexmedetomidine in neurosurgical patients showed that lumbar CSF pressure did not alter in patients undergoing transsphenoidal pituitary surgery who received dexmedetomidine,<sup>[255]</sup> but MAP, heart rate and CPP were all reduced. The cardiovascular effects result from a reduced central sympathetic output.<sup>[256]</sup> Clearly, further studies are required to investigate the usefulness of dexmedetomidine in head injury.

Clonidine has been investigated in head-injured patients for its role in reducing catecholamine release and causing cerebral vasoconstriction, rather than as a sedative. In a study of seven patients 3–5 days after severe head injury, clonidine administration caused a significant reduction in plasma noradrenaline (norepinephrine) and adrenaline (epinephrine) concentrations with no change in global cerebral perfusion.<sup>[257]</sup> This was thought to be due to  $\alpha_2$ -adrenoceptor blockade in the medulla. A further study demonstrated no effect on ICP, CBF or cerebral metabolism of a bolus of clonidine in head-injured patients.<sup>[258]</sup> In recent years, clonidine has been used in the 'Lund' protocol. This is a method of treating head injury that avoids the use of therapies to raise MAP, a manoeuvre that theoretically increases cerebral oedema by increasing the hydrostatic forces across cerebral blood vessels.<sup>[259,260]</sup> The cerebral haemodynamic tolerance to clonidine in severe head injury was investigated in one study, showing a reduction in MAP and CPP with little associated change in ICP in most patients, while in three patients there was a significant but transient

increase in ICP sufficient to cause a profound fall in jugular bulb venous oxygen saturation.<sup>[261]</sup>

## 10. Antipsychotics

Antipsychotics act as dopamine antagonists within the CNS. Their actions are sedative, antipsychotic and antiemetic. They tend to be used to sedate agitated patients, for instance to reduce the effects of drug withdrawal syndromes during weaning from mechanical ventilation, or to allow radiological imaging. Drugs in this class include butyrophenones, phenothiazines and thioxanthenes. They have the advantage of rendering the patient calm without major respiratory depression.

### 10.1 Butyrophenones

The butyrophenones include haloperidol and droperidol. Haloperidol acts within 30–60 minutes of an intravenous dose and its effects last 4–8 hours.<sup>[262]</sup> It has an elimination half-life of 21 hours. Droperidol has a more delayed onset of action, attributed to its higher molecular weight and extensive protein binding, which inhibit its passage into the CNS. It also has a longer duration of action of 2–24 hours, which may be due to avid receptor binding.<sup>[263]</sup> Both drugs are metabolised by the liver.

Butyrophenones can cause hypotension because of  $\alpha$ -adrenergic blockade.<sup>[264]</sup> In the CNS, droperidol was found to produce a slight fall in ICP in patients with head injury in whom ICP was raised.<sup>[265]</sup> This may be due to the decrease in CBF as a result of cerebral vasoconstriction, which was discovered in dogs.<sup>[266]</sup> Haloperidol use was not associated with an improved outcome following head injury in humans, and was associated with a longer period of amnesia.<sup>[267]</sup> Other adverse effects include extrapyramidal effects,<sup>[268,269]</sup> neuroleptic malignant syndrome<sup>[270]</sup> and, in high doses, prolonged QT interval and torsade de pointes.<sup>[271]</sup>

### 10.2 Phenothiazines

Phenothiazines are not only dopamine antagonists but also have antiadrenergic and anticholinergic effects. Chlorpromazine, promazine and thioridazine are the most frequently used agents in this category. Because of their antipsychotic action in addition to sedation, they are most widely used to

treat confusional states in which agitation is a major feature.<sup>[272]</sup> As with the butyrophenones, phenothiazine therapy can cause hypotension, extrapyramidal adverse effects and the neuroleptic malignant syndrome. While these agents may have a role in confusional states, there are no data to support the use of antipsychotics for routine sedation in head-injured patients.

### 10.3 Phenothiazines

Phenothiazines are not only dopamine antagonists they also have anti-adrenergic and anticholinergic effects. Chlorpromazine, promazine and thioridazine are the most commonly used drugs in this class. Due to their antipsychotic action in addition to sedation, they are most widely used to treat confusional states where agitation is a major feature.<sup>[272]</sup> As with the butyrophenones, phenothiazines therapy can cause hypotension, extrapyramidal adverse effects and the neuroleptic malignant syndrome. While these agents may have a role in confusional states, there are no data to support the use of antipsychotics for routine sedation in head-injured patients.

### 10.4 Atypical Antipsychotics

Recent publications report early experience with the, use of risperidone for post-traumatic confusional states.<sup>[273,274]</sup> While this agent appears to be effective, its eventual role in this setting remains to be defined.

### 10.5 Summary

The antipsychotics are commonly used to control agitation in head injured patients, but there is little data to choose between individual agents. A recent supplement addresses this issue in the setting of agitation in the ICU,<sup>[275]</sup> but provides limited guidance for their administration to neurotrauma patients, in whom such drugs can unavoidably confound neurological assessment. The avoidance of respiratory depression and cardiovascular stability are particular concerns.

## 11. Conclusion

There is no ideal sedative for use in head injury and there are few studies that directly compare the effectiveness and adverse effects of different agents

in this group of patients. Among the existing drugs, propofol appears to have most of the properties required but, as with all commonly used agents, this is at the expense of systemic blood pressure. It also has a number of potential problems associated with its formulation. The other frequently used agents, such as opioids and benzodiazepines, also have features to recommend them. In the absence of new, improved drugs, sedation of head-injured patients is likely to continue to involve a number of agents. The introduction of remifentanyl is promising, with its unique metabolic pathway allowing intense narcosis with a rapid and reliable offset of action, and the potential neuroprotective action of dexmedetomidine is worthy of further study.

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Correspondence and offprints: Dr David K. Menon, Addenbrooke's Hospital, Box 93, Cambridge, CB2 2QQ, UK.  
E-mail: dkm13@wbic.cam.ac.uk