

# Effect of midazolam versus propofol sedation on markers of neurological injury and outcome after isolated severe head injury: a pilot study

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Head injury is the leading cause of mortality in young patients and often has a devastating neurological outcome.<sup>1,2</sup> A substantial proportion of victims die, and many others have permanent disability. The outcome after severe head injury is determined by both the primary and secondary brain injuries. The management of patients with head injury aims to prevent, limit and treat the process that leads to secondary brain injury.

Midazolam is commonly used as a sedative in intensive care units, partly because of its favourable pharmacokinetic properties.<sup>3</sup> In critically ill trauma patients, propofol has been compared with midazolam as a sedative in terms of safety and efficacy.<sup>4</sup> However, the neuroprotective effects of the two drugs have not been studied in terms of the biochemical markers of brain injury.

Glial cell S100 $\beta$  protein has been extensively studied as a marker of brain injury. Increased serum concentrations of S100 $\beta$  are associated with adverse neurological outcome after stroke,<sup>5,6</sup> subarachnoid haemorrhage,<sup>7,8</sup> and coronary artery bypass graft surgery.<sup>9,10</sup> Nitric oxide (NO) has numerous functions in human physiology<sup>11</sup> and plays an important role in the pathophysiology of ischaemic brain injury.<sup>12</sup> After head injury in humans, increased concentrations of NO in cerebrospinal fluid (CSF) and plasma are associated with early injury severity.<sup>13</sup>

We conducted a prospective, double-blind, randomised trial:

- to compare serum S100 $\beta$  and plasma NO concentrations during the first 5 days after ICU admission between patients with isolated severe head injury who received a midazolam-based sedation regimen and those who received a propofol-based regimen; and
- to assess the association between these S100 $\beta$  and NO concentrations and neurological outcome 3 months later.

## Methods

The study was approved by the institutional ethics committee in May 2003, and written informed consent was obtained from the first-degree relatives of 30 patients with head injury. Inclusion criteria were patient age, 18 to

## ABSTRACT

**Background:** Midazolam and propofol are sedative agents commonly administered to patients with brain injury. We compared plasma concentrations of glial cell S100 $\beta$  protein and nitric oxide (NO) between patients who received midazolam and those who received propofol sedation after severe brain injury, and investigated the association between S100 $\beta$  and NO concentrations and neurological outcome.

**Design:** 28 patients with severe head injury (Glasgow Coma Score <9) who required sedation and ventilation were randomly assigned to receive midazolam ( $n = 15$ ) or propofol ( $n = 13$ ) based sedation. Blood samples were drawn daily for 5 days for estimation of S100 $\beta$  and NO concentrations. Neurological outcome was assessed 3 months later as good (Glasgow Outcome Score [GOS], 4–5) or poor (GOS, 1–3).

**Results:** A good neurological outcome was observed in 8/15 patients (53%) in the midazolam group and 7/13 patients (54%) in the propofol group. Patients with a poor outcome had higher serum S100 $\beta$  concentrations on ICU admission and on Days 1–4 in the ICU than those with a good outcome (mean [SD] on Day 1, 0.99 [0.81] v 0.41 [0.4]  $\mu\text{g/L}$ ; Day 2, 0.80 [0.81] v 0.41 [0.24]  $\mu\text{g/L}$ ; Day 3, 0.52 [0.55] v 0.24 [0.25]  $\mu\text{g/L}$ ; and Day 4, 0.54 [0.43] v 0.24 [0.35]  $\mu\text{g/L}$ ;  $P < 0.05$ ). There was no significant difference on Day 5. Plasma NO concentrations were not associated with outcome. In subgroup analysis, there was no difference in S100 $\beta$  and NO concentrations between patients with a good outcome versus those with a poor outcome in either the midazolam or propofol group.

**Conclusions:** Plasma concentrations of markers of neurological injury in patients with severe head injury were similar in those who received midazolam sedation and those who received propofol. Patients who had a poor neurological outcome at 3 months had consistently higher serum S100 $\beta$  concentrations during the initial 4 days after injury than patients who had a good outcome.

**Table 1. Treatment of increased intracranial pressure**

- Increased sedation or analgesia with bolus midazolam, propofol and/or morphine (as described in *Methods* section).
- Mannitol (0.5–1 mg/kg; maximum of 240 g or serum osmolality > 310 mmol).
- Vecuronium boluses if needed for muscle paralysis, if above measures fail. ◆

**Table 2. Glasgow Outcome Scale for classification of neurological outcome**

- |   |   |
|---|---|
| 5 | Good recovery, resumption of life despite minor deficits  |
| 4 | Moderate disability (but not dependent), able to travel by public transport, able to work in public sheltered setting |
| 3 | Severe disability, dependent on others for activities of daily living   |
| 2 | Persistent vegetative state   |
| 1 | Dead ◆  |

65 years, isolated head injury with post-resuscitation score on the Glasgow Coma Scale (GCS)<sup>14</sup> less than 9, and requirement for mechanical ventilation. Exclusion criteria were multiple trauma, previous organic brain disease or brain surgery, renal or hepatic failure, body mass index greater than 32 kg/m<sup>2</sup>, spinal cord injury, pregnancy, and substance abuse identified at the time of ICU admission.

After initial stabilisation in the ICU, patients were randomly allocated (using a sealed envelope technique) to receive either a midazolam or propofol intravenous infusion for sedation. Midazolam was given at the rate of 0.1–0.3 mg/kg per hour, and propofol at the rate of 1.5–5 mg/kg per hour. Both groups received morphine sulfate (0.1–0.2 mg/kg per hour) as per study protocol.<sup>4,15</sup> Additional boluses of morphine (0.07–0.1 mg/kg) or fentanyl (2–3 µg/kg) were administered when clinically indicated by patient discomfort, such as tachypnoea, tachycardia, hypertension or coughing. The administration of fluid, vasopressors and neuromuscular blocking agents, and catheter insertion for monitoring of intracranial pressure (ICP) were at the discretion of the treating physicians. No specific protocol was applied for tight glycaemic control. Raised intracranial pressure (> 20 mmHg for over 10 minutes) was treated<sup>15</sup> as outlined in Table 1.

Prognostic indicators,<sup>15</sup> comprising post-resuscitation GCS, systemic hypotension (systolic blood pressure < 90 mmHg), and hypoxia (arterial oxygen tension < 8 kPa [60 mmHg]) during the first 24 hours of hospitalisation, were recorded. The computed tomography (CT) scan

obtained on initial admission to hospital was analysed by an independent investigator and classified as:<sup>15</sup>

- perimesencephalic cistern effacement;
- diffuse swelling;
- diffuse swelling with midline shift greater than 4 mm;
- diffuse injury with punctuated haemorrhages; or
- subarachnoid haemorrhage, evacuated mass lesions or multiple contusion.

Mean daily measurements of ICP and cerebral perfusion pressure (CPP), and total time that ICP was greater than 20 mmHg, and CPP was less than 70 mmHg, were recorded. Mean daily arterial blood pressure, central venous pressure and rectal temperature were also recorded, as was the use of neuromuscular blocking agents, barbiturates and vasopressors. Other routine ICU investigations, including full blood count, plasma urea, creatinine and electrolyte concentrations, and blood coagulation indices were recorded daily to monitor organ function. Adequacy of ventilation was monitored by routine chest x-ray and serial arterial blood gas analysis. Patients were evaluated daily for signs and symptoms of sepsis according to the sepsis criteria described by Parillo et al.<sup>16</sup>

Arterial blood samples were taken for measurement of S100β and NO concentration at the time of ICU admission and daily for 5 days thereafter. Neurological outcome was assessed 3 months after injury using the Glasgow Outcome Scale (GOS; Table 2<sup>17</sup>) by an independent investigator who was blinded to treatment groups. Outcome was reported as good (GOS, 4–5) or poor (GOS, 1–3).

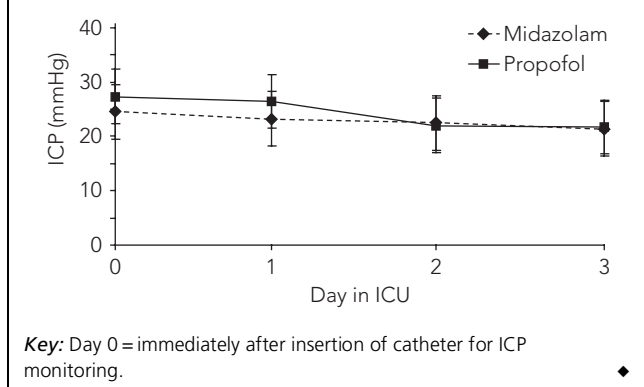
#### S100β concentration

S100β concentration was analysed using a monoclonal two-site immunoradiometric assay (AB Sangtec Medical, Bromma, Sweden), using three monoclonal antibodies: SMST12, SMSK25 and SMSK28. These antibodies detect the S100β isoforms αβ and ββ, which are specific for astroglial cells. Serum samples were diluted with phosphate buffer and incubated with plastic beads coated with the monoclonal antibodies. During incubation, S100β was bound to the antibody-coated beads. After 1 hour of incubation, the beads were washed to remove any unbound material and incubated with <sup>125</sup>I-labelled anti-S100β antibody, which binds to the S100β captured by the beaded antibody. After 2 hours of incubation and subsequent washing, the amount of radioactive label bound to S100β was measured with a gamma counter. The limit of sensitivity of the kit is 0.02 µg/L.

#### Nitric oxide products

Concentration of the products of nitric oxide (nitrate and nitrite) was determined using a Sievers 280 NOA chemiluminescent analyser (Sievers Instruments, Boulder, Col,

**Figure 1. Mean daily intracranial pressure (ICP), by drug used for sedation**



USA). In solution, NO reacts with molecular oxygen to form nitrite ( $\text{NO}_2^-$ ), and with oxyhaemoglobin and superoxide anion ( $\text{O}_2^-$ ) to form nitrate ( $\text{NO}_3^-$ ). By adding acid and reducing agents, nitrate and nitrite are converted to NO. An inert gas is then used to purge NO from the solution for subsequent detection by chemiluminescence. The detector is based on the reaction of NO with ozone ( $\text{O}_3$ ), which produces nitrogen dioxide in an excited state ( $\text{NO}_2^*$ ) and molecular oxygen. The excited state of  $\text{NO}_2^*$  decays to give an infrared chemiluminescence above 600 nm. Light emission is directly related to the NO content of the sample. Sodium nitrate and nitrite were used as standards.

### Statistical analyses

Data were expressed as mean and standard deviation (SD). Continuous variables were compared between groups by analysis of variance or Student's *t* test. Differences in non-parametric data, such as GCS or CT finding, were assessed by Mann-Whitney U test. A *P* value < 0.05 was considered significant.

### Results

Thirty patients with severe head injury were enrolled in the study. Two patients in the propofol group were withdrawn from the study as they received propofol for less than 10 hours. The causes of brain injury in the remaining 28 were: road traffic accident (18 patients [64%]), fall from a height (8 [28%]), and assault (2 [8%]).

The midazolam and propofol groups were similar in terms of ICP (Figure 1), use of vasopressors (Table 3). They were also similar in age, GCS, type of injury and treatment (Table 3). More patients in the midazolam group had multiple contusions on initial CT scan. The time from initial injury to entry into the study (defined by the commencement of

**Table 3. Characteristics of 28 patients with severe head injury, by drug used for sedation**

Characteristic	Midazolam (n = 15)	Propofol (n = 13)
Mean time from injury to ICU admission (h) (SD)	12.86 (3.5)	9.07 (5.76)
Mean duration of sedative administration (h) (SD)	50.0 (29.35)	52.5 (20.4)
Median post-resuscitation GCS (range)	4.73 (3–7)	5.07 (3–7)
Male to female ratio	15:1	13:0
Cause of injury: no. (%)		
Road traffic accident	10 (67%)	8 (62%)
Fall	4 (31%)	4 (27%)
Assault	1 (8%)	1 (7%)
Management: no. (%)		
Vasopressors	9 (60%)	8 (61%)
Neuromuscular blocking agents	5 (33%)	5 (38%)
Mannitol	8 (53%)	6 (46%)
Decompressive craniotomy*	10 (66%)	10 (77%)
Insertion of ICP monitoring	12 (80%)	10 (76%)
Phenytoin	4 (26%)	3 (23%)
CT diagnosis on admission: no. (%)		
Compressed cisterns	4 (31%)	4 (27%)
Diffuse axonal swelling with or without midline shift	8 (53%)	8 (62%)
Evacuated haematomas (all)		
Epidural haematoma	1 (7%)	2 (15%)
Subdural haematoma	5 (33%)	5 (38%)
Intracerebral bleed	2 (13%)	3 (23%)
Multiple contusions*	9 (60%)	5 (38%)

\* *P* < 0.05. GCS = Glasgow Coma Score. ICP = intracranial pressure. CT = computed tomography.

midazolam or propofol sedation) was (mean  $\pm$  SD) 10.7  $\pm$  5.2 h and was similar in the two groups (12.8  $\pm$  5.7 h [midazolam] v 9.0  $\pm$  3.3 h [propofol]).

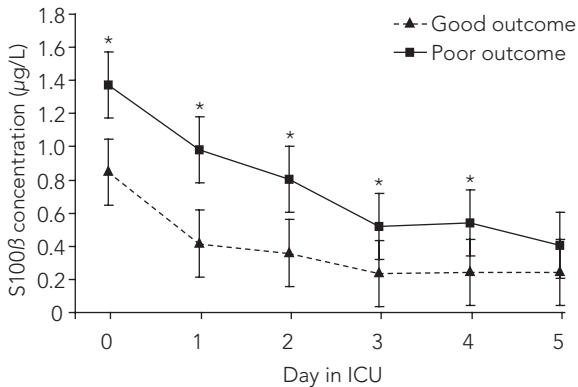
### Neurological outcome and biochemical markers

A good neurological outcome (GOS, 4–5) was observed in 8/15 patients (53%) in the midazolam group and 7/13 patients (54%) in the propofol group. Of the patients who had a poor neurological outcome (GOS, 1–3), eight died (midazolam, 3/15 [20%] v propofol, 5/13 [38%]; *P* = 0.07), and five (17%) had severe disability (midazolam, 3/15 (20%) v propofol, 2/13 (15%); *P* = 0.8).

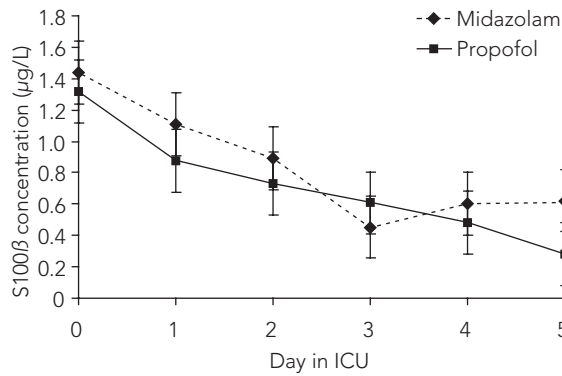
Patients who had a poor neurological outcome at 3 months had a higher mean serum S100 $\beta$  concentration on admission to the ICU than those who had a good outcome

**Figure 2. Serum S100 $\beta$  concentrations after severe head injury**

**A. By neurological outcome**

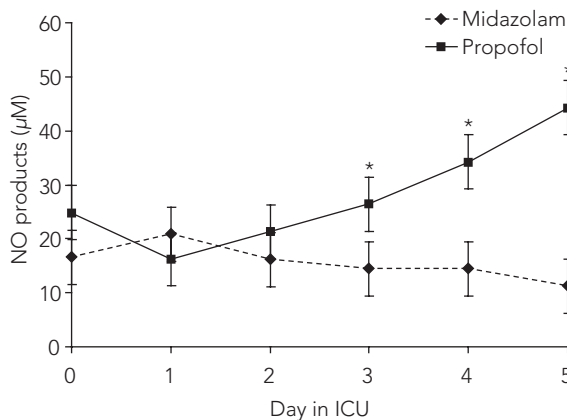


**B. In poor neurological outcome group, by drug used**



\*  $P < 0.05$  for comparison of good and poor outcome groups.

**Figure 3. Plasma concentration of nitric oxide products in the poor neurological outcome group, by drug used for sedation**



\*  $P < 0.05$  for comparison of midazolam and propofol groups.

( $1.37 \pm 0.77$  v  $0.84 \pm 0.74$   $\mu\text{g/L}$ ;  $P = 0.04$ ). They also had higher S100 $\beta$  concentrations on Days 1–4 after ICU admission (Figure 2A).

Mean plasma concentration of NO products was similar in patients with subsequent good and poor neurological outcomes, both at the time of ICU admission ( $20.41 \pm 13.2$  v  $20.01 \pm 10.3$   $\mu\text{M}$ ;  $P = 0.7$ ) and over the ensuing 5 days.

**Effect of midazolam and propofol on biochemical markers**

In the patients with a poor outcome, serum S100 $\beta$  concentrations were similar in the midazolam and propofol groups at each time point (Figure 2B). However, plasma concentration of NO products was greater in those given propofol than in those given midazolam on Days 3–5 after ICU admission (Day 3,  $26.36 \pm 8.4$  v  $14.45 \pm 7.34$   $\mu\text{M}$ ; Day 4,  $34.21 \pm 10.5$  v  $14.43 \pm 6.22$   $\mu\text{M}$ ; and Day 5,  $44.28 \pm 12.22$  v  $11.67 \pm 6.3$   $\mu\text{M}$ ;  $P < 0.05$ ) (Figure 3).

**Discussion**

Our most important finding was that serum S100 $\beta$  concentrations in the first 4 days after severe head injury were higher in patients who had a poor neurological outcome than in those who had a good outcome. Neurological outcome was similar in those who received midazolam and those who received propofol for sedation. Concentrations of S100 $\beta$  and NO products were also similar in patients who received midazolam and those who received propofol.

Anaesthetic drugs can affect ischaemic and traumatic brain injury by numerous mechanisms, and their potential for neuroprotection is clinically relevant.<sup>18</sup> Midazolam and propofol are the commonly used sedatives in the ICU,<sup>19</sup> but differ in their efficacy, safety and cost–benefit profiles in sedating ICU patients.<sup>15,19,20</sup> Kelly et al showed statistical differences in ICP and CPP measurements between patients with head injury given opioids and those given propofol sedation, but no significant difference in long-term clinical outcome.<sup>15</sup> When used for long-term ICU sedation, propofol has been associated with more systemic adverse effects than midazolam.<sup>15,19</sup> In our study, haemodynamic parameters were similar in patients who received midazolam and those who received propofol. Three other studies that compared propofol and midazolam for short-term sedation in patients with moderate to severe brain injury showed that, after 24 hours' infusion, there was no difference in ICP and CPP.<sup>19,21</sup>

The recovery time (to extubation) was shorter after short-term sedation with propofol compared with midazolam.<sup>19,21</sup> In patients with trauma, long-term sedation with propofol is associated with increased plasma lipid content,<sup>22</sup> and greater degree of failure to achieve target sedation<sup>21</sup> when

compared with midazolam. However, achieving desired sedation differs between head injury and trauma patients, because of the presence of brain pathology and difficulty in monitoring in the former.<sup>23</sup>

Benzodiazepines, barbiturates and propofol inhibit neuronal activity through the action of  $\gamma$ -aminobutyric acid (GABA).<sup>24</sup> In healthy volunteers, midazolam decreased cerebral blood flow and rate of cerebral oxygen utilisation to 22%–43% of baseline.<sup>25</sup> It has also been shown that enhancement of GABA activity decreases the excitotoxic neuronal damage that follows neuronal injury. Receptor activation by GABA and GABA agonists increases chloride conductance, which reduces neuronal excitability. Both basic scientific and clinical data support the hypothesis that enhancement of GABA activity can produce neuroprotection.

S100 $\beta$  is a useful marker of the severity of brain injury in both minor and severe brain injury.<sup>26</sup> Increased serum S100 $\beta$  concentrations have been associated with poor neurological outcome in brain injury.<sup>6–9</sup> Woertgen and colleagues found, similarly to our study, that S100 $\beta$  concentrations increase as early as 24 hours after injury and are predictive of neurological outcome after severe brain injury, but they did not assess the effects of sedative drugs.<sup>26</sup> In our study, S100 $\beta$  concentrations were higher for up to 4 days after injury in patients who had a subsequent poor neurological outcome compared with those who had a good outcome. We found no difference in serum concentration of S100 $\beta$  between the midazolam and propofol groups.

Nitric oxide production increases at all stages of cerebral ischaemia.<sup>12</sup> Increased concentrations of NO products during brain ischaemia might be a useful marker of the severity of injury. However, our study found no association. This is consistent with the result of Clark and colleagues.<sup>13</sup> NO probably has protective and injurious functions at different times after brain ischaemia, and in response to different magnitudes of injury. Among patients with a poor neurological outcome, those who received propofol had higher concentrations of NO products on Days 3–5 than those who received midazolam. However, it is not possible to conclude that either drug has a neuroprotective or pharmacokinetic effect from these limited data. A larger study might show a clinical significance of this finding.

We did not measure CSF concentrations of S100 $\beta$  and NO products, but such measurements might reveal their value as markers of brain injury. A further limitation of our study was the inability to assess level of sedation achieved, as no reliable scoring system exists to measure sedation in patients with brain injury.

## Conclusions

- The serum concentrations of markers of neurological injury were similar in patients with severe head injury who received midazolam sedation and those who received propofol.
- Serum S100 $\beta$  concentrations were higher in the group of patients who had a poor neurological outcome at 3 months compared with the group who had a good outcome.
- Plasma NO concentrations were similar in patients with a poor outcome and those with a good outcome.

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## References

- 1 Jennett B, MacMillan R. Epidemiology of head injury. *BMJ* 1981; 282: 101-4.
- 2 Lee KH, Angus DC, Abramson NS. Cardiopulmonary resuscitation: what cost to cheat death? *Crit Care Med* 1996; 24: 2046-52.
- 3 Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; 62: 310-24.
- 4 Sanchez-Izquierdo-Riera JA, Caballero-Cubedo RE, Perez-Vela LJJ, et al. Propofol versus midazolam: safety and efficacy for sedating the severe trauma patients. *Anesth Analg* 1998; 86: 1219-24.
- 5 Büttner T, Weyers S, Postert T, et al. S100 protein: serum marker of focal brain damage after ischemic territorial MCA infarction. *Stroke* 1997; 28: 1961-5.
- 6 Fassbender K, Schmidt R, Schreiner A, et al. Leakage of brain-originated proteins in peripheral blood: temporal profile and diagnostic value in early ischemic stroke. *J Neurol Sci* 1997; 148: 101-5.
- 7 Persson L, Hardemark H, Edner G, et al. S-100 protein in cerebrospinal fluid of patients with subarachnoid hemorrhage. A potential marker of brain injury. *Acta Neurochir (Wien)* 1988; 93: 116-22.

- 8 Wiesmann M, Missler U, Hagenstrom H, Gottmann D. S100 protein plasma levels after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)* 1997; 139: 1155-60.
- 9 Ali MS, Harmer M, Vaughan R. Serum S100 protein as a marker of cerebral damage during cardiac surgery. *Br J Anaesth* 2000; 85: 287-98.
- 10 Westaby S, Johnsson P, Parry AJ, et al. Serum S100 protein: a potential marker for cerebral events during cardiopulmonary bypass. *Ann Thorac Surg* 1996; 61: 88-92.
- 11 Faraci FM, Brian JE Jr. Nitric oxide and the cerebral circulation. *Stroke* 1994; 25: 692-03.
- 12 Iadecola C. Bright and dark sides of nitric oxide in ischemic brain injury. *Trends Neurosci* 1993; 20: 132-9.
- 13 Clark R, Kockanek P, Obrist W, et al. Cerebrospinal fluid and plasma nitrite and nitrate concentrations after head injury in humans. *Crit Care Med* 1996; 24: 1243-51.
- 14 Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; 2: 81-4.
- 15 Kelly FD, Goodale BD, Williams J, et al. Propofol in the treatment of moderate and severe head injury a randomized, prospective double blind pilot trial. *J Neurosurg* 1999; 90: 1042-52.
- 16 Parillo JE, Parker MM, Natanson C, et al. Septic shock in human: advances in the understanding of pathogenesis, cardiovascular dysfunction and therapy. *Ann Intern Med* 1990; 113: 227-42.
- 17 Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28: 14-20.
- 18 McIntosh TK, Juhler M, Wieloch T. Novel pharmacologic strategies in the treatment of experimental traumatic brain injury: 1998. *J Neurotrauma* 1998; 15: 731-69.
- 19 Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in intensive care unit: a systematic review. *JAMA* 2000; 283: 1451-9.
- 20 Sandiumenge Campus A, Sanchez-Izquierdo Riera JA, Toral Vazquez D, et al. Midazolam and 2% propofol in long-term sedation of traumatized critically ill patients. Efficacy and safety comparison. *Crit Care Med* 2000; 28: 3612-9.
- 21 Carrasco G, Molina R, Costa J, et al. Propofol vs midazolam in short, medium and long term sedation of critically ill patients: a cost-benefit analysis. *Chest* 1993; 103: 557-64.
- 22 Gottardis M, Kühnl-Brady KS, Koller W, et al. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *Br J Anaesth* 1989; 62: 393-6.
- 23 Hansen-Flaschen J, Cowen J, Palomano RC. Beyond the Ramsay scale; Need for a validated measure of sedation drug efficacy in the intensive care unit. *Crit Care Med* 1994; 22: 732-3.
- 24 Hollrigel GS, Toth K, Soltesz I. Neuroprotection by propofol in acute mechanical injury: role of GABAergic inhibition. *J Neurophysiol* 1996; 76: 2412-22.
- 25 Forster A, Juge O, Morel D. Effect of midazolam on cerebral blood flow in human volunteers. *Anesthesiology* 1982; 56: 453.
- 26 Woertgen C, Rothoerl RD, Holzschuh M, et al. Comparison of serial S-100 and NSE serum measurements after severe head injury. *Acta Neurochir (Wien)* 1997; 139: 1161-5. □