Effects of propofol on cerebral oxygenation and metabolism after head injury


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Background. Flow-metabolism coupling is thought to be deranged after traumatic brain injury, while the effects of propofol on flow-metabolism coupling are controversial. We have used a step increase in target plasma propofol concentration in head injured patients to explore flow-metabolism coupling in these patients.

Methods. Ten patients with a moderate to severe head injury received a step increase in propofol target controlled infusion of 2 μg ml⁻¹. Cerebral tissue gas measurements were recorded using a multimodal sensor, and regional chemistry was assessed using microdialysis. Arterial-jugular venous oxygen differences (AVDO₂) were measured and all patients had cortical function monitoring (EEG).

Results. The step increase in propofol led to a large increase in EEG burst-suppression ratio (0% (range 0⁻1.1) to 46.1% (range 0⁻61.7), P<0.05); however, this did not significantly change tissue gas levels, tissue chemistry, or AVDO₂.

Conclusions. Flow-metabolism coupling remains intact during a step increase in propofol after traumatic brain injury. The EEG burst-suppression induced by propofol after traumatic brain injury does not appear to be a useful therapeutic tool in reducing the level of regional ischaemic burden.

Br J Anaesth 2003; 91: 781–6

Keywords: anaesthetics i.v., propofol; brain, metabolism; complications, head injury

Accepted for publication: July 15, 2003

Propofol is used widely as a sedative agent in neurosurgical critical care because it is generally assumed that it has properties that are advantageous to the injured brain. Propofol is believed to maintain, or even improve, cerebral autoregulation; indeed even high doses of this drug do not obtund autoregulation or carbon dioxide reactivity.

The effect of propofol on flow-metabolism coupling is more controversial, with at least one study demonstrating intact coupling. However, a number of reports suggest that flow-metabolism coupling may be adversely influenced by propofol, and both increases and decreases in cerebral oxygen extraction have been demonstrated with propofol. Despite the fact that normal flow-metabolism coupling is believed to be retained in only a proportion of head injured patients there is a paucity of data regarding the influence of propofol on flow-metabolism coupling after traumatic brain injury. Equally, although high dose barbiturates are believed to be of benefit in head-injured patients with refractory intracranial hypertension there is a lack of data looking at how propofol induced EEG burst-suppression influences cerebral oxygenation and metabolism.

Recent technical advances have allowed the development of implantable sensors that can measure regional tissue oxygenation (e.g. Neurotrend sensor, Codman, USA) and regional tissue chemistry (microdialysis). The Neurotrend sensor can also measure local carbon dioxide (PbCO₂), pH, and temperature. Brain tissue oxygen probes and cerebral microdialysis increasingly are being used as monitoring tools in head-injured patients, both to aid the diagnosis of secondary injury and to guide therapeutic interventions. Both tools provide continuous monitoring of brain physiology and therefore have a potential role in defining pathophysiology within a region of interest.
Brain tissue oxygen monitors measure the local partial pressure of oxygen in the brain extracellular space ($P_{\text{bO}_2}$). $P_{\text{bO}_2}$ reflects the local balance between oxygen supply and demand, with $P_{\text{bO}_2}$ falling as either the supply (cerebral blood flow or arterial oxygen content) falls or the demand (cerebral metabolic rate of oxygen) increases. The arterial–jugular venous oxygen difference (AVDO2) reflects the global balance between oxygen supply and demand. Because $P_{\text{bO}_2}$ and AVDO2 measurements both assess the relationship between oxygen supply and demand they can be used as surrogate markers of flow-metabolism coupling.

Microdialysis is a technique for collecting samples of extracellular fluid; substrate and metabolite molecules (e.g. glucose, lactate, pyruvate, and glycerol) can then be analysed. Lactate and pyruvate concentrations are thought to reflect anaerobic and aerobic metabolism, respectively, with the lactate/pyruvate ratio being considered an important marker of the redox state of the tissue. Glycerol is thought to be a marker of cell membrane breakdown, whilst glucose levels represent a complicated balance between local blood flow, peripheral blood concentration, and cellular uptake.\(^{13}\)

We have combined microdialysis and tissue oxygen monitoring to investigate how a step increase in blood propofol concentration affects the relationship between cerebral oxygenation and metabolism after traumatic brain injury. Our hypothesis was that in non-ischaemic areas of the brain flow-metabolism coupling would remain intact; however, in ischaemic areas of the brain increased metabolic suppression would improve the ischaemic burden.

### Methods

This study was approved by the local research ethics committee and written informed assent was obtained from the next of kin of all patients. Patients older than 16 yr with moderate to severe head injury requiring sedation, ventilation, and intracranial pressure monitoring were eligible for the study. Patients with coagulation disorders, unstable physiology, or who had received barbiturates or benzodiazepines for sedation were excluded.

Patients were managed according to Addenbrooke’s Neurosciences Critical Care Unit protocols,\(^{14,15}\) which include sedation with propofol and fentanyl, paralysis with atracurium, and support of cerebral perfusion pressure (CPP) to approximately 70 mm Hg. Monitored variables included ECG, peripheral oxygen saturation, end-tidal carbon dioxide, jugular venous oxygen saturation, and intracranial pressure. Apart from the propofol intervention, all other aspects of physiology were kept as stable as possible during the study.

### Intracranial monitoring

Every patient had a microdialysis catheter (Gold tipped CMA 70 10-mm membrane, CMA, Stockholm, Sweden) and Neurotrend™ catheter (Codman, Raynham, MA, USA) inserted into the frontal cerebral parenchyma, in conjunction with an intracranial pressure sensor (Codman, Raynham, MA, USA) using a triple-lumen cranial access device (TechniCam, UK).\(^6\) The microdialysis catheter was inserted to a depth of 30 mm and the Neurotrend™ sensor was inserted to a depth of 45 mm; these depths were calculated so that predominantly white matter was being monitored, and that the oxygen sensor on the Neurotrend™ catheter was monitoring at approximately the same region as the microdialysis catheter. The catheters were inserted at least 4 h before the intervention studies took place and the positions of the probes were defined by obtaining a computed tomography (CT) scan of the head.

### Microdialysis

The microdialysis catheter was perfused with Ringer’s solution (K$^+$ 4 mmol litre$^{-1}$, Na$^+$ 147 mmol litre$^{-1}$, Ca$^{2+}$ 2 mmol litre$^{-1}$, Cl$^-$ 155 mmol litre$^{-1}$) at a rate of 0.3 μl min$^{-1}$ using the CMA106 pump (CMA, Stockholm, Sweden). Vials were changed at approximately 30-min intervals and were placed onto dry ice and stored at −70°C for later analysis. The delay from the microdialysis membrane to the collecting vial (dead space) is 17 min, and this was accounted for in the study design.

Microdialysis samples were analysed for glucose, lactate, pyruvate, and glycerol using a CMA600 bedside microdialysis analyser (CMA, Stockholm, Sweden).

### Cortical function monitoring

EEG burst-suppression, defined as bursts of high amplitude theta/delta activity with intervening periods of electrical quiescence, was measured using continuous cortical function monitoring (band-pass 0.1–70 Hz). During each target propofol concentration, the duration (milliseconds) of electrical quiescence vs high amplitude theta/delta activity was measured in order to calculate the burst-suppression ratio. Where a characteristic EEG burst-suppression pattern was absent a burst suppression ratio of 0% was scored.

### Propofol intervention

All patients received propofol (Diprivan 2%, AstraZeneca UK Ltd, UK) using a target controlled infusion pump (Master TCI UK, Fresenius Vial S.A., France), incorporating ‘Diprifusor’ software for at least 4 h before the study. All target concentrations during this time were stable and in the range of 2 μg ml$^{-1}$, corresponding to infusion rates of approximately 3–4 mg kg$^{-1}$ h$^{-1}$. For each patient, the dose targeted was that which resulted in an infusion rate of propofol similar to the infusion rate being used before the target infusion was commenced. This dose range is within the range specified in the treatment algorithm of our unit. This target concentration was then
used as the baseline concentration for the first part of the study. For the second half of the protocol a propofol plasma target concentration 2 μg ml⁻¹ above the baseline target concentration was used, corresponding to infusion rates of approximately 6–8 mg kg⁻¹ h⁻¹. Any reductions in arterial pressure that occurred when the propofol dose was increased were treated primarily with i.v. colloid infusion but norepinephrine was used if this was not sufficient. At least 20 min were allowed for the propofol concentration to reach the new target concentration before measurements for the second part of the protocol were begun. Using the ‘Diprifusor’ software this time span is sufficient to ensure that not only the blood but also the brain concentration has equilibrated with the new dose.¹⁷

Each target plasma propofol concentration was maintained for at least 47 min, during which time microdialysis dialysate was collected, the first 17 min of dialysate having been discarded. During the last 12 min of the period PbO₂ data were collected and averaged, and paired arterial and jugular venous bloods were taken for calculation of the arterial-venous oxygen gradient (AVDO₂).

Apart from minor adjustments to the norepinephrine infusion rate, which were made in order to keep the CPP stable, and minor adjustments to ventilation, which were made in order to keep end-tidal carbon dioxide stable, no other interventions were made during either the baseline period or the CPP augmentation period.

### Oxygen reactivity test

We have developed this method of PbO₂ correction based on the linear relationship that exists between PbO₂ and PaO₂ when PaO₂ is within the normal or hyperoxic range.¹⁸¹⁹ With propofol maintained at the upper target concentration, a baseline PbO₂ and PaO₂ was recorded. The inspired fraction of oxygen FIO₂ was then increased by one or two steps; after each step PbO₂ and PaO₂ were again recorded after a 15-min period of equilibration. The PbO₂ and PaO₂ values at the different FIO₂ levels were used to calculate a linear regression equation relating PbO₂ to PaO₂. Using this equation, PbO₂ changes that resulted from changes in PaO₂ could be corrected.

### Data analysis

Brain tissue oxygen data were downloaded onto a personal computer using customized software.²⁰ Mean PbO₂ values were recorded over 4-min time periods.

The data were analysed using StatView 4 (SAS, Cary, NC, USA) and presented as median (range). Statistical comparisons were made using the Wilcoxon signed rank test with Bonferroni corrections made for multiple comparisons. Correlations were defined using linear regression analysis.

### Results

Ten patients were studied (seven men, three women). The median age was 36 yr (range 21–53) and the median admission Glasgow Coma Score was 7 (range 3–9). The propofol target concentration at baseline was 2.2 (1.8–2.9) μg ml⁻¹ and at the higher level 4.2 (3.8–4.9) μg ml⁻¹. The PacO₂ was comparable at both concentrations of propofol (4.8 (3.9–5.1) vs 4.8 (3.9–5.2) kPa), as was the CPP (71 (65–87) vs 71 (66–89) mm Hg).

The pattern of injury was classified as evacuated mass lesion in eight patients and as diffuse injury in two patients. Five patients had large bilateral lesions on CT scan. In eight of the patients, a craniectomy had been performed for evacuation of a subdural haematoma (n=6) or large haemorrhagic contusion (n=2). In the five patients who had predominantly unilateral pathology, intracranial pressure, Neurotrend™ and microdialysis monitors were sited in the injured hemisphere in two patients. Studies were performed 3 (2–5) days after injury. In one patient the microdialysis and Neurotrend™ probes were sited in tissue that appeared oedematous on CT scans; however, we were unable to site a jugular bulb catheter in this patient and microdialysis data were unavailable because of failure of the catheter. In one patient there was insufficient dialysate to analyse glycerol levels. Subsequent data analysis is therefore based on PbO₂ data from 10 patients, AVDO₂ data from nine patients, and microdialysis data from nine patients (glycerol, eight patients).

Baseline and interventional physiological data are shown in Tables 1 and 2.

Increases in target propofol concentrations resulted in varying degrees of burst suppression in all but one of the

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**Table 1** Intracranial pressure (ICP), electroencephalogram burst-suppression ratio (BSR), arterial-venous oxygen difference (AVDO₂), brain tissue oxygen (PbO₂), brain tissue carbon dioxide (PbCO₂), and brain tissue pH (Br pH) responses to a 2 μg ml⁻¹ step increase in target propofol concentration. Corrected PbO₂ values are corrected for any change that occurred in the arterial partial pressure of oxygen (PaO₂). Data are presented as median (range) with P<0.05 being treated as significant and non-significant results displayed as NS.

<table>
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<tr>
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<th>ICP (mm Hg)</th>
<th>BSR (%)</th>
<th>AVDO₂ (ml litre⁻¹)</th>
<th>PaO₂ (kPa)</th>
<th>PbO₂ (uncorrected) (kPa)</th>
<th>PbO₂ (corrected) (kPa)</th>
<th>PbCO₂ (kPa)</th>
<th>Br pH</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>13.5 (10.2–19.8)</td>
<td>0 (0–1.1)</td>
<td>21 (12–45)</td>
<td>12.7 (9.9–17.6)</td>
<td>3.0 (1.2–3.7)</td>
<td>3.0 (1.2–3.7)</td>
<td>6.1 (4.6–6.5)</td>
<td>7.2 (6.9–7.3)</td>
</tr>
<tr>
<td>Propofol intervention</td>
<td>12.8 (8.8–19.7)</td>
<td>46.1 (0–61.7)</td>
<td>20 (10–46)</td>
<td>13.9 (12.3–17.2)</td>
<td>3.2 (1.2–5.3)</td>
<td>3.1 (1.2–4.5)</td>
<td>5.9 (4.5–6.4)</td>
<td>7.2 (6.9–7.3)</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>P&lt;0.05</td>
<td>NS</td>
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patients studied; however, despite this evidence of significant increase in metabolic suppression there were no significant changes in regional or global physiology.

Basal regional and global physiology did not predict changes in physiology during the propofol intervention. In one patient, in whom baseline $PbO_2$ was in the ischaemic range at baseline (1.2 kPa), there was no clinically significant improvement in $PbO_2$ despite a large increase in the burst suppression ratio (from 0 to 51%). Three patients had baseline lactate/pyruvate ratios above normal limits (>27), however, the ratio did not improve significantly despite a significant increase in burst suppression ratio.

### Discussion

We have used target controlled infusions of propofol with a step increase in the target concentration to investigate whether flow-metabolism coupling remains intact after traumatic brain injury, and whether metabolic suppression, over and above the normal level of sedation, leads to a reduction in ischaemic burden. The results of this study show that there are no significant changes in cerebral physiology with increased metabolic suppression and indicate that flow-metabolism coupling is intact.

An understanding of the significance of our data requires an assessment of the context for these results along with a consideration of the methodological issues involved. We addressed these issues using AVDO$_2$ and $PbO_2$ monitoring, which provide a measure of the relationship between oxygen supply and demand, on a global and regional basis, respectively. We did not show a significant change in either variable, despite a significant suppression of metabolism, suggesting that flow-metabolism coupling is intact in our patients and that propofol does not adversely affect this coupling after traumatic brain injury. This result is in line with a study examining the response of middle cerebral artery flow velocity and jugular venous saturation to EEG suppression in patients undergoing acoustic neuroma resection. In that study jugular bulb saturations did not change, despite reduced cerebral blood flow velocities and increased EEG burst suppression, indicating that flow-metabolism coupling remained intact.

However, the literature provides a basis for suspecting that flow-metabolism coupling might be deranged in our patient population. Closed head injury is known to disrupt this relationship, at least in a proportion of patients. Obrist and colleagues concluded that 45% of head-injured patients exhibit hyperaemia (‘luxury perfusion’) based on measurements of AVDO$_2$ and global cerebral blood flow, whilst Lee and colleagues concluded that up to 97% of head injured patients have evidence of deranged flow metabolism-coupling compared with healthy controls.

Further, several studies suggest that the pharmacological intervention that we used (high dose propofol) may itself have intrinsic vasoactive properties that disrupt flow-metabolism coupling. At least four human studies have concluded that propofol does disrupt flow-metabolism coupling, with both intrinsic cerebral vasoconstricting and vasodilating properties having been suggested. Two studies have concluded that propofol may reduce cerebral blood flow to a greater extent than it reduces CMRO$_2$, that is that propofol has direct vasoconstricting properties and may actually cause cerebral ischaemia. Jansen and colleagues found that in patients undergoing brain tumour surgery there was a significantly lower jugular saturation in patients anaesthetized with propofol than in a matched group anaesthetized with nitrous oxide and isoflurane; however, they did not find a significant difference in AVDO$_2$. Nandate and colleagues compared jugular saturations in three groups of patients undergoing coronary artery bypass grafting and found a significant decrease in jugular bulb saturation 1 h after normothermic cardio-pulmonary bypass with propofol anaesthesia but not with isoflurane or sevoflurane anaesthesia. In contrast, two other studies have come to the opposite conclusion, and shown a reduction in oxygen extraction during propofol anaesthesia, indicating that propofol suppresses metabolism to a greater extent than it suppresses blood flow during cardio-pulmonary bypass and during induction of anaesthesia in healthy patients.

As far as we are aware there is only one other human study examining the effects of propofol-induced EEG burst suppression in head-injured patients. In this study an infusion of propofol, titrated to achieve a degree of EEG burst suppression, led to a significant reduction in intracranial pressure and a significant increase in jugular bulb saturation. Together with evidence that cerebral blood flow did not decline as much as expected during metabolic suppression, the authors concluded that flow-metabolism coupling was disorder.
In the light of these conflicting findings, it is important that we consider other possible interpretations of our data. Theoretically our results could be interpreted as resulting from a combination of hyperaemia as a result of disordered flow-metabolism coupling and direct vasoconstriction by propofol. These two processes, when combined, could counteract each other, and result, on average, in no overall change in regional and global oxygen supply–demand relationships. However, such an explanation would demand perfect matching of the two opposing effects across the patients that we studied. This seems unlikely.

It is also important to consider whether our data have an impact on therapies that we use in the context of closed head injury. High dose barbiturates are believed to be useful in the management of refractory intracranial hypertension after traumatic brain injury, however, their use is not recommended for prophylaxis. None of our patients had an intracranial pressure greater than 20 mm Hg and so we are unable to comment on the use of high dose propofol for refractory intracranial hypertension. However, our data certainly suggest that, in the absence of refractory intracranial hypertension, EEG burst suppression using propofol is not a useful therapeutic tool even in areas of the brain that appear to be ischaemic within the time frame of our studies. It is possible that metabolic suppression could result in amelioration of the ischaemic burden in injured tissue over a longer time frame, but our data do not address this possibility. Furthermore, we were unable to determine whether burst-suppression with propofol offers protection for tissue that is not yet ischaemic but, which is at risk of secondary insults. Failure of propofol to reduce ischaemic burden is in line with other data suggesting that EEG burst suppression achieved with propofol does not reduce the incidence of jugular bulb desaturations during cardiopulmonary bypass, however, we were able only to study a small number of patients and we are aware of the possibilities of a type II statistical error in our negative findings.

In conclusion, our data suggest that after traumatic brain injury flow-metabolism coupling remains intact during a step increase in propofol infusion rates. Using propofol to achieve EEG burst-suppression does not appear to be a useful therapeutic tool in reducing the level of ischaemic burden in the short-term.

Acknowledgements

Dr Andrew Johnston is supported by a grant from Codman. Dr Luzius Steiner is supported by a Myron B. Laver Grant (Department of Anaesthesia, University of Basel, Switzerland) and grants from the Margarete und Walter Lichtenstein-Stiftung (Basel, Switzerland) and the Swiss National Science Foundation. He is recipient of an Overseas Research Student Award (Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom). Dr Jonathan Coles is a Wellcome research training fellow and recipient of a Beverley and Raymond Sackler Studentship Award. Work of the department is supported by a grant from the Medical Research Council (Grant No. G 9439390 I50833). The authors thank AstraZeneca UK Ltd for the loan of the TCI pump and Dr Mark O’Connell for help with microdialysis analysis.

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