Hypoalbuminaemia and propofol pharmacokinetics

Editor—Cavaliere and colleagues report that hypoalbuminaemia does not affect the accuracy of Diprifusor during sedation with propofol.1 They hypothesized that hypoalbuminaemia may affect the accuracy of target-controlled infusion (TCI) by introducing major deviations in propofol pharmacokinetics. Their results, however, failed to show significant differences in the accuracy of the Diprifusor between hypo- and normoalbuminaemic patients. A possible explanation for these results is that the effect of hypoalbuminaemia may be too small in relation to the overall degree of accuracy achieved by TCI devices. A second mechanism could be that propofol binds to albumin linearly in the range of concentrations tested in this study.

We reported that a twofold increase in the concentration of unbound propofol occurred without alteration in the total propofol concentration in blood during cardiopulmonary bypass (CPB).2 This increase was caused mainly by a lower concentration of albumin. Furthermore, we showed that the mean value of the hepatic extraction ratio was greater than 0.8 and remained constant throughout the study despite the increase of unbound fraction. There was no significant difference in the total body clearance of propofol before, during and after CPB and concluded that hypoalbuminaemia does not affect the accuracy of Diprifusor.

For drugs that are restrictively cleared, regardless of route of administration, an increase in the unbound fraction leads to accelerated total body clearance and reduced total concentration. The unbound concentration at steady state is unchanged since an increase in the unbound concentration gradually returns to the control value after redistribution.3 Thus the ultimate effect of changes in protein binding is only transient.

In contrast, for drugs that are non-restrictively cleared and administered i.v., an increase in the unbound fraction could not affect total body clearance as such drugs are extracted by the eliminating organ so efficiently that protein binding does not limit their removal. The total concentration at steady state is unchanged and an increase in the unbound fraction leads to an immediate and sustained increase in the unbound concentration. This is of clinical significance for highly protein-bound drugs with narrow therapeutic indices, such as propofol.4 Cavaliere and colleagues also reported that no increase in the sedative effect of propofol was apparent. Target concentrations were adjusted to achieve a Ramsay sedation score between 4 and 5 and were similar in the hypoalbuminaemic and normoalbuminaemic patients. However, the increase of unbound propofol without alteration in the total propofol concentration in blood might occur as a result of the hypoalbuminaemia as we demonstrated in our study.5 Further study of the pharmacodynamics of propofol in hypoalbuminaemic patients is required.

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Editor—We are grateful to Dr Takizawa and colleagues for their interest in our paper on the influence of hypoalbuminaemia on Diprifusor performance during sedation with propofol.1 They studied propofol unbound and total concentration in blood and hepatic extraction rate before, during, and after CPB.2 In their letter they point out that: (i) propofol total concentration did not change (apart from an initial decrease) during CPB, while the unbound fraction increased; such increase was probably consequent to dilutional hypoalbuminaemia and indicates that unbound fraction can be affected by albumin levels (i.e. that albumin does not bind propofol linearly); (ii) propofol hepatic extraction rate and total body clearance did not change during CPB in spite of dilutional hypoalbuminaemia; this would suggest that hypoalbuminaemia does not affect propofol pharmacokinetics and, as a consequence, cannot affect Diprifusor performance.3,4

We think their data are very interesting but not applicable to the conditions of our study on sedation in ICU patients. Firstly, propofol mean concentration was very different in the two studies (1 vs 2.5 μg ml⁻¹), and albumin may bind propofol linearly at lower propofol concentrations and non-linearly at higher ones. In addition, acute haemodilution by CPB priming is a condition quite different from chronic hypoalbuminaemia; for example, unbound fraction, calculated as the ratio of unbound to total propofol concentrations in whole blood, may have been affected by haematocrit changes. Finally, unchanged hepatic extraction ratio does not rule out significant changes of propofol pharmacokinetics associated with CPB, which have been reported by other authors.5

We agree that an increase of propofol pharmacological effects should be expected in relation with an increase of unbound propofol concentration. Such effect was not pointed out in our study, but may be measurable with instruments more sensitive than clinical judgement.

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Bispectral index monitoring may not reliably indicate cerebral ischaemia during awake carotid endarterectomy

Editor—We read with interest Dr Deogaonkar’s group’s work on the use of the bispectral index (BIS) for detection of cerebral ischaemia during carotid endarterectomy.1 Multi-channel electroencephalography (EEG) is certainly a valuable tool in detecting cerebral ischaemia, though its complexity requires a neurologist or neurologist-supervised technician for interpretation, which adds considerable expense. If a simple, easy to use processed EEG
could be adequate to diagnose ischaemia and provide the answer to the ‘shunt or not shunt’ clinical question, this device would be a valuable tool, indeed.

We recently were involved in the care of a patient who developed signs of intraoperative cerebral ischaemia during awake carotid endarterectomy performed under cervical plexus block. Some of our ‘awake’ carotid endarterectomy procedures are converted to a general anesthetic if the patient’s mental status deteriorates or if the regional anesthetic is insufficient. Therefore, we use the PSA 4000 with the PArray® (PSA) (Physiometics Inc., North Billerica, MA, USA) as an adjunctive monitor to better titrate the depth of anesthesia. In these cases the PSA is used during the entire procedure. The PSA, like the BIS, uses the EEG and a complex algorithm to derive the Patient State Index (PSI), a number from 0–100 that is intended to be a guide to anesthetic depth. Unlike the BIS, which uses a single channel monopolar EEG to derive the BIS value, the PSA utilizes four channel (Fp1, Fp2, Cz, Pz), multi-regional, multi-frequency, power and coherence relationships and its own unique algorithm to arrive at the PSI value. There have been case reports that the PSA, like the BIS, can detect global cerebral ischaemic events. Often, even focal cerebral hyperperfusion manifests with large regional or even global EEG changes. Additionally, there are some data that suggest that as few as two channels are necessary to detect cerebral ischaemia during carotid endarterectomy.

Our patient was a 56-yr-old male with severe left internal carotid artery stenosis (80–99% stenosis) and moderate right internal carotid artery stenosis (50–79% stenosis). After placing a cervical plexus block and until the time of carotid cross-clamp, the patient was awake and alert, with a PSI value of 95–98. The monitor was set to display the raw EEG waves during the case, which were predominantly alpha and beta waves on both the left and right. Shortly after left carotid cross-clamp, the patient’s mental status deteriorated and his right hand grip strength was markedly diminished. Interestingly, the PSI value dropped to 85 after 2 min and the raw EEG showed delta and theta waves on both the left and right—a dramatic change from just moments before. Haemodynamics were unchanged.

It would appear that the BIS, as Deogaonkar and colleagues state, lacks the sensitivity to adequately detect cerebral ischaemia and detect the restoration of cerebral electrical activity once perfusion is reestablished. This monitor was certainly not designed for such a purpose. However, PSA may offer advantages over the BIS in having multi-channel analysis and the ability to compare raw EEG from the left and right hemispheres, thus the potential for the PSA to detect cerebral ischaemia may be much higher. Further study with the PSA in this area may be worth pursuing.

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Editor—Thank you for the opportunity to respond to the letter regarding our article. We are interested to see Culp and colleagues confirm our observation that the BIS does not detect unilateral (ipsilateral) ischaemia during awake carotid endarterectomy. It is interesting that more detailed EEG analysis by the PSA device might be more sensitive than BIS. However, form of monitoring is utilized, there is nothing more sensitive than the patient’s neurological status during awake endarterectomy. It is for this reason that the awake procedure offers the highest sensitivity and specificity for ischaemia while no other monitoring procedure has achieved this sensitivity. We have previously reported the specificity and sensitivity of jugular venous oxygen saturation monitoring during awake carotid endarterectomy. Of all the forms of intraoperative monitoring that have been compared with ischaemia in awake patients during carotid endarterectomy the SJV02 had the highest sensitivity and specificity. Transcranial Doppler has also been evaluated but it is not tolerated well in awake patients because of the need to maintain pressure on the temporal bone constantly throughout the procedure. Careful studies using sophisticated electrophysiology as used in the case reported by Culp and colleagues need to be evaluated in a large series of patients before they can be universally accepted.

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Safety of transtracheal jet ventilation in upper airway obstruction

Editor—We read with interest the article by Chandradeva and colleagues, who reported the use of percutaneous transtracheal jet ventilation (PTJV) in the emergency management of two patients with severe upper airway obstruction. We agree that this is an extremely useful technique for this situation but would like to suggest that the method they employed could be further enhanced by the use of an automated jet ventilator with end-expiratory pressure monitoring linked to a pause function. We have used this technique in two situations similar to those described in their article.

Case 1, a 64-yr-old man undergoing tracheostomy because of worsening episodes of stridor secondary to a vocal cord palsy after radiotherapy for malignant neck lymphadenopathy. He was given a small dose of midazolam and then an inhalational induction was attempted using sevoflurane in oxygen 100%. During induction the patient developed worsening stridor, and became restless. His arterial oxygen saturation began to fall, at which point the anaesthetist abandoned the gas induction and called for help. Stridor and hypoxia persisted despite discontinuing the volatile agent. At this point a second anaesthetist inserted a 14G Ravussin jet ventilation catheter (VBM, Germany) through the criocothyroid membrane under local anaesthesia, and the patient’s lungs were oxygenated with PTJV. We used an automatic jet ventilator (Mistral model, Acutronic, Switzerland), and delivered oxygen (FIO2=1) with initial settings of: driving pressure=1 bar (15 psi), frequency=30 min−1, and pause pressure=20 cm H2O. This led