Hypoalbuminaemia does not impair Diprifusor performance during sedation with propofol

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Background. About 98% of plasma propofol is bound to albumin. We investigated if severe hypoalbuminaemia may affect the accuracy of a target-controlled infusion (TCI) device, the Diprifusor, during sedation in critically ill patients.

Methods. Ten critically ill hypoalbuminaemic patients (<24 g litre\(^{-1}\)) and 10 critically ill normoalbuminaemic patients (>32 g litre\(^{-1}\)) were included in this study. They underwent sedation with propofol, aimed at a Ramsey sedation score of 4–5. The Diprifusor was used to achieve target propofol plasma concentrations that ranged between 0.6 and 1.5 mg litre\(^{-1}\). Propofol concentration was measured by high-performance liquid chromatography 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after starting TCI. The accuracy of TCI was evaluated by calculating performance errors \[\text{PE} = 100 \times (\text{measured concentration} - \text{predicted concentration})/\text{predicted concentration}\], absolute and relative individual median performance errors (MDAPE and MDPE) and divergence (the slope of individual regression lines between PEs and time).

Results. PEs [median (range)] were −7 (−65, 79) in hypoalbuminaemic patients and −2 (−53, 188) in normoalbuminaemic patients; absolute PEs were 21 (1, 79) and 22 (0, 188). No significant difference was observed between the two groups. MDPE, MDAPE and divergence values were also similar. In most patients the accuracy of TCI increased with time because higher PE values were observed during the first 30 min.

Conclusions. Hypoalbuminaemia does not affect the accuracy of Diprifusor during sedation with propofol in critically ill patients.


Keywords: anaesthetics i.v., propofol; complications, hypoalbuminaemia; infusion, target controlled; sedation

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The Diprifusor, a commercially available device for target controlled infusion (TCI) of propofol,\(^{1,2}\) has been employed recently for sedation in critically ill patients.\(^{3}\) In TCI, a computer drives the infusion pump and regularly resets the infusion rate on the basis of a pharmacokinetic model to achieve a preset concentration of the drug in blood.\(^{4}\) The Diprifusor\(^{\text{TM}}\) has been in routine use in anaesthesia for the last 5 yr.\(^{5,6}\) Any major individual deviations from normal propofol pharmacokinetics can result in large differences between target and actual concentrations. Such deviations in propofol pharmacokinetics may be caused by physiological derangements in critically ill patients. Consequently, the use of the Diprifusor in these patients may be associated with higher degrees of inaccuracy.

Hypoalbuminaemia, one of the frequently observed physiological derangements in critically ill patients, can affect the pharmacokinetics of drugs that strongly bind to albumin.\(^{7–10}\) Usually 98% of plasma propofol is bound to this protein,\(^{11,12}\) but the unbound fraction may increase in the presence of hypoalbuminaemia, as suggested by studies performed \textit{in vitro} on plasma from critically ill patients.\(^{12}\) Consequently, it seemed useful to verify the degree of accuracy of the Diprifusor in the presence of low plasma albumin concentrations. The aim of this study was to
Methods

This study was performed in the general intensive care unit of the Catholic University of Rome Hospital. After obtaining approval from the local research ethics committee and informed consent from the patients or their next of kin, 20 patients who needed sedation and had plasma albumin concentrations <24 g litre⁻¹ (n=10) or >32 g litre⁻¹ (controls; n=10) were enrolled. All the patients had arterial and central venous catheters in place and the lungs were ventilated mechanically. Patients’ physical characteristics, plasma albumin concentration and diagnosis at admission were recorded. The exclusion criteria were age ≤18 or ≥70 yr, reported allergy to propofol or its components or to colloids, obesity [body mass index (BMI >30)], hypotension (systolic arterial pressure <120 mm Hg or mean arterial pressure <70 mm Hg), significant liver damage (total bilirubin >3.4 µmol litre⁻¹), alanine aminotransferase test (ALT) or aspartate aminotransferase test (AST) ≥30% of the normal upper limit), renal impairment (plasma creatinine >176 µmol litre⁻¹) or clinically appreciable peripheral oedema or increased third space volume (i.e. large pleural or peritoneal effusions).

Each patient was sedated with propofol; this was given through the central venous catheter using Diprifusor TCI (Zeneca, UK). The target concentration was set at 1 mg litre⁻¹ initially; subsequently, it was adjusted to achieve a Ramsey sedation score between 4 (a brisk response to a light glabellar tap) and 5 (a sluggish response to a light glabellar tap). Each patient was weighed and the calculated weight was used for TCI calculations. Before starting the sedation, patients were questioned for pain and, if required, morphine was given in small bolus doses of 1–2 mg i.v. until satisfactory analgesia was obtained [the patient scored 1 or 2 on a scale between 1 (no pain) and 5 (maximal pain)]. In addition, colloids 8–10 ml kg⁻¹ were given to prevent arterial hypotension. During sedation, if systolic arterial pressure decreased to <90% of the pre-sedation values, normal saline 0.5–1 litre was given. Persistent hypotension was treated with small doses of a vasoconstrictor (etilefrine hydrochloride, 1–2 mg i.v.).

The first 8 h of sedation was taken for this study. Monitoring consisted of heart rate, arterial pressure, respiratory rate and pulse oximetry. Nine heparinized arterial blood samples were collected: one before TCI and the others 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after starting TCI. Blood was rapidly centrifuged and plasma was stored at −60°C. Total propofol concentration was determined by high-performance liquid chromatography using Plummer’s method after solid–liquid extraction with Oasis cartridges (Waters, USA). Plasma albumin was measured in the pre-sedation blood sample by the central laboratory of the hospital using a colorimetric assay (ALB plus; Roche Diagnostics, Germany) using a Roche/Hitachi 917 analyser. Coefficients of variation of propofol and albumin estimations were 4.9 and 3.0% respectively.

The performance error (PE) corresponding to each sample was calculated as PE = 100×[(measured concentration–target concentration)/target concentration].

In each subject, median absolute performance error (MADPE) was calculated as the median of the absolute PE values, i.e. ignoring positive or negative signs, and median performance error (MDPE) was calculated as the median of PEs calculated with positive and negative signs maintained. MDPE was taken to indicate bias (i.e. the systematic tendency to under- or overestimate the measured concentration); MDAPE was taken to indicate inaccuracy, providing information on the typical size of the differences between measured and targeted concentrations. The divergence, i.e. the slope of the regression line between PE and the time elapsed from starting TCI, was taken to indicate time-related changes in predicting TCI. In comparison with crude PE and absolute PE (APE) values, MDPE, MDAPE and divergence are not influenced by within-subject variance.

Statistical analysis was performed using the software Statistica for Windows (StatSoft, USA). Data were tested for normality by examination of histograms and by the Shapiro–Wilk test and were accordingly reported as mean (SD) or median (range). Comparisons were performed using the Mann–Whitney U test.

A priori power analysis for planning sample size was performed with the software G*Power obtained from the University of Düsseldorf’s website. We assumed that hypoalbuminaemia would increase the Diprifusor’s inaccuracy by at least 50% of the standard deviation of the population and would consequently have a significant impact on clinical practice, i.e. we arbitrarily decided to search for a medium size effect according to Cohen’s convention. In power analysis this corresponds to choosing a value of 0.5 for parameter d, defined as the ratio between the difference of the two means and the standard deviation of the population. The analysis was first applied to an independent t-test with equal group sizes and equal σ, and this showed that, to achieve a power (1−β) of 0.851 with α=0.05, it was necessary to compare 146 samples (73 vs 73). Then the sample size was corrected for the Mann–Whitney U-test by dividing 146 by the asymptotic relative efficiency (or Pitman efficiency) of the U-test, which is 0.955. The final sample size was 152.

Results

All the patients enrolled in this study completed the 8-h TCI without side-effects; in three hypoalbuminaemic patients and two controls, saline infusion was required to maintain the systolic arterial pressure >90% of the initial value. None of the patients required administration of vasoconstrictors. In seven hypoalbuminaemic and six control patients the targeted concentration was 1 mg litre⁻¹ during the study. The range of concentrations selected in each patient is
Individual PE and APE trends are shown in Figure 2. PE values in controls and APE values in both groups showed significant deviations from the normal distribution. PEs were \(-65, 79\) in hypoalbuminaemic patients and \(-53, 188\) in controls; corresponding APEs were 21 (1, 79) and 22 (0, 188). PE and APE values in the two groups did not differ significantly. A tendency towards larger performance errors was observed during the first 30 min in many patients. Particularly high PE and APE values (188 and 174%) were observed in one normoalbuminaemic patient 5 and 15 min after starting TCI; in the same subject, successive determinations showed improved TCI accuracy.

MDPE, MDAPE and divergence were similar in hypoalbuminaemic and normoalbuminaemic patients (Table 2). MDPE did not show the presence of a systematic bias, but spread over a wide range of values, suggesting that large systematic errors were frequent in patients of both groups. MDAPE values were similar to those reported by others.5 In most patients, divergence had a negative sign, reflecting higher predictive errors during the first 30 min of TCI; divergence was positive only in one hypoalbuminaemic patient and in two controls.

### Discussion

About 98% of serum propofol is bound to albumin, while negligible fractions are linked to lipoproteins or to \(\alpha_1\)-acid glycoprotein.6,7 We hypothesized that hypoalbuminaemia may affect the accuracy of TCI by introducing major deviations in propofol pharmacokinetics. Our results, however, failed to show significant differences in the accuracy of the Diprifusor between hypoalbuminaemic and normoalbuminaemic patients. In both groups, MDPE and MDAPE were acceptable according to the commonly adopted criteria for TCI device validation.17

Hypoalbuminaemia is frequently observed in critical illness and results from transcapillary leak, decreased synthesis, large losses of body fluids and dilution caused by fluid resuscitation. Although albumin has several functions, such as maintaining colloid osmotic pressure in the vascular system, transporting fatty acids and bilirubin, and scavenging free radicals,18 correction of hypoalbuminaemia by albumin administration has not decreased the risk of death; in fact it has been associated with increased mortality.18 We did not correct hypoalbuminaemia in patients included in this study because to do so is considered unnecessary and potentially dangerous.19,20 Nevertheless, some workers suggest that severe hypoalbuminaemia (<20 g litre\(^{-1}\)) should be corrected21 and that albumin infusion may decrease fluid requirements and tissue oedema.22 Septic patients, who were excluded from this study, may also represent an exception and benefit from albumin administration.23,24

Hypoalbuminaemia may affect both the pharmacodynamics and the pharmacokinetics of drugs that are highly bound to albumin.7–10 By increasing the free drug concentration in plasma, hypoalbuminaemia may increase the drug

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**Table 1** Patient physical characteristics, new Simplified Acute Physiology Score (SAPS II), plasma albumin concentration, diagnosis on admission, and targeted concentrations of propofol. BMI, body mass index; TC, target concentrations, reported as medians (range); COPD, chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>SAPS II</th>
<th>BMI (kg m(^2))</th>
<th>Albumin (g litre(^{-1}))</th>
<th>Diagnosis</th>
<th>TC (mg litre(^{-1}))</th>
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<tr>
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<tr>
<td>1</td>
<td>53</td>
<td>F</td>
<td>34.2</td>
<td>23.1</td>
<td>22</td>
<td>Post-anoxic coma</td>
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<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>22.1</td>
<td>24.8</td>
<td>19</td>
<td>Stroke</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>29.3</td>
<td>29.8</td>
<td>18</td>
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</tr>
<tr>
<td>4</td>
<td>51</td>
<td>F</td>
<td>39.1</td>
<td>24.8</td>
<td>23</td>
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<tr>
<td>5</td>
<td>61</td>
<td>F</td>
<td>40.2</td>
<td>28.4</td>
<td>21</td>
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</tr>
<tr>
<td>6</td>
<td>70</td>
<td>F</td>
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<td>28.7</td>
<td>23</td>
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<td>7</td>
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<td>F</td>
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<td>22.0</td>
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<td>8</td>
<td>66</td>
<td>F</td>
<td>26.2</td>
<td>22.5</td>
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<td>Post-surgical respiratory failure</td>
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<td>M</td>
<td>35.1</td>
<td>26.0</td>
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<td>Stroke</td>
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<td>10</td>
<td>58</td>
<td>M</td>
<td>33.6</td>
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<tr>
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<td>F</td>
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<td>(5.9)</td>
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<td>Controls (plasma albumin &gt;32 g litre(^{-1}))</td>
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<td>34</td>
<td>COPD, respiratory failure</td>
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<tr>
<td>4</td>
<td>37</td>
<td>M</td>
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<td>22.0</td>
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</tr>
<tr>
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<td>63</td>
<td>F</td>
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<td>38</td>
<td>F</td>
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<td>7</td>
<td>58</td>
<td>M</td>
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<tr>
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<td>F</td>
<td>30.6</td>
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reported in Table 1. The propofol concentrations are reported in Figure 1.
concentration at effect sites and enhance the pharmacological actions. In this study, however, no increase in the sedative effect of propofol was apparent because targeted concentrations were similar in the two groups.

The pharmacokinetic effects of low plasma albumin are mainly related to the changes in clearance and distribution of the drug. Renal clearance usually parallels free drug concentration because only the unbound drug is filtered by the glomerulus and high free drug concentrations may increase tubular secretion. Also, hepatic clearance may be affected by changes of free drug concentrations, but usually hepatic blood flow and intrinsic clearance of unbound drug have larger influence. Theoretically, TCI inaccuracy resulting from abnormal drug clearance may not be immediately evident, but may become apparent later, when the influence of drug distribution is less pronounced. By contrast, in this study we observed a downward trend in TCI inaccuracy, which suggested that propofol clearance was not appreciably affected, although 8 h was probably not long enough to get conclusive data in this regard. Other studies have also reported larger Diprifusor inaccuracy initially after starting TCI, and have hypothesized that this might be caused by incomplete mixing.

Hypoalbuminaemia usually increases the volume of distribution of drugs highly bound to albumin and this may potentially affect TCI accuracy. For TCI systems, the target concentration is kept constant by keeping the content of the central compartment constant. Such content is calculated by multiplying the targeted concentration by the estimated volume of the central compartment. If the propofol central compartment had been increased in hypoalbuminaemic patients, a bias would have been apparent towards measured drug concentrations being lower than targeted concentrations, i.e. towards negative predictive errors. By contrast, in this study no significant bias of Diprifusor accuracy was seen in either group.

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. The power of this study was adequate to show a medium-sized effect, i.e. an effect that is at least equal to half the standard deviation of the population. Swinhoe and colleagues reported a standard deviation of APE of about 42% in a study on Diprifusor accuracy. Assuming that the standard deviation of the population is near this value, a medium-sized effect of hypoalbuminaemia would correspond to a difference of 21 in APE between hypoalbuminaemic and normoalbuminaemic patients. Although this difference may appear large, we thought that a lower effect would not be of clinical importance, given the large variability of PE.

A second possible mechanism could be that propofol binds to albumin linearly in the range of concentrations tested in this study. Hypoalbuminaemia does not affect the pharmacokinetics of drugs that are highly, but linearly bound to albumin because the percentage of free drug is unaffected. The relationship between bound and free propofol in plasma has not been investigated in relation to albumin concentrations, but only to changes in total propofol concentration. This relationship was not linear and free propofol percentage increased by 30% (from 1.2 to 1.7%) from the lowest (0.5 mg litre$^{-1}$) to the highest propofol concentrations tested (16 mg litre$^{-1}$). Nevertheless, the relationship can be regarded as linear in the lower part of the curve, suggesting non-saturable binding sites at concentrations up to two- or three-fold higher than those used for sedation. A low-capacity, high-affinity site primarily involved at total concentrations lower than 10–20 mg litre$^{-1}$ may compensate for a loss of global capacity for propofol binding.

In conclusion, this study shows that, during sedation with propofol, the accuracy of the Diprifusor is unaffected in the
TCI in hypoalbuminaemic patients

presence of hypoalbuminaemia, although our data cannot entirely rule out the risk of a loss of precision in long-term sedation. Further studies are needed to evaluate Diprifusor accuracy in hypoalbuminaemic patients at higher propofol concentrations, such as those used during anaesthesia.

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