Pharmacokinetics of propofol during conscious sedation using target-controlled infusion in anxious patients undergoing dental treatment


Summary
Infusion of propofol by a target-controlled infusion (TCI) system is effective in achieving conscious sedation for anxious patients presenting for dental surgery. It is a common clinical observation that anxious patients require more anaesthetic drugs than non-anxious individuals. In study 1 we have defined blood propofol concentrations necessary for conscious sedation in both anxious (n = 23) and non-anxious (n = 18) patients. The pump performance of the TCI system, using Gepts’ pharmacokinetic model, was evaluated in these two patient groups. Subsequently, clearance of propofol was compared in the two groups. Mean measured venous serum propofol concentrations obtained between 20 and 35 min after the optimal sedation level was reached were 1.6 (± 0.2) µg ml⁻¹ in the anxious patients compared with 1.7 (± 0.3) µg ml⁻¹ in the control group (study 1) and 1.4 (± 0.27) µg ml⁻¹ in study 2. The pump systematically overpredicted measured propofol concentrations in both groups (study 1). There was no significant difference in propofol clearance between the two groups. In study 2, an optimized set of microconstants was derived which should more accurately predict the pharmacokinetic profile of the anxious population and this set was tested prospectively in another group of 12 anxious dental patients. Bias and precision with the optimized kinetic set were significantly less than the values obtained in study 1. We conclude that there was no significant pharmacokinetic differences between anxious and non-anxious subjects receiving subanaesthetic doses of propofol for conscious sedation. (Br. J. Anaesth. 1998; 80: 324–331)

Keywords: anaesthetics i.v.; propofol; pharmacokinetics, propofol; surgery, dental; psychological responses

When administered in subanaesthetic doses, propofol has useful sedative and anxiolytic properties. Infusion of propofol by a target-controlled infusion (TCI) system has been shown to be effective in achieving conscious sedation for extremely anxious and mentally handicapped patients presenting for dental surgery. A TCI system consists of a computer-controlled infusion pump which uses pharmacokinetic models in the calculation and delivery of infusion regimens required to theoretically achieve and maintain stable concentrations of drug in the patient. The first objective of this study was to define the blood propofol concentrations necessary for conscious sedation in both anxious and non-anxious patients presenting for dental chair surgery. It is a common clinical supposition that anxious patients have a greater requirement for anaesthetic drugs than non-anxious patients and we wished to establish if there was a difference between the two groups in the target concentrations at which satisfactory sedation conditions were achieved. The second objective of the study was to evaluate the performance of a target-controlled propofol infusion system using the three-compartment pharmacokinetic model proposed by Gepts and colleagues during conscious sedation in these two patient groups. We subsequently analysed the relationship between measured serum propofol concentrations and the drug input regimens used by the TCI system in the two patient populations and determined and compared the clearance of propofol in the two groups. Thereafter, we derived an optimized set of microconstants which should, at least in theory, more accurately predict the pharmacokinetic profile of the anxious patient population. In a second study the performance of this refined kinetic set was tested prospectively in another 12 anxious subjects undergoing similar dental procedures (study 2).

Patients and methods
The study was approved by the Institutional Ethics Review Board of the Academic Hospital, University of Amsterdam. Children, pregnant women, patients aged more than 65 yr or ASA III or IV, or body mass index > 28 kg m⁻² were excluded from the study. Use

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of concomitant medication, abuse of alcohol and allergy to propofol or soya beans were additional criteria for exclusion.

**STUDY 1**

We studied 23 patients (12 females, 11 males) (anxious group), ASA I or II, undergoing routine dental chair procedures. All gave informed consent to undergo the procedure under conscious sedation with propofol. These patients had been referred to the clinic because of inability to comply with dental surgery without sedation because of associated anxiety. All patients fulfilled the criteria for anxiety, as assessed using the unidimensional Corah’s dental anxiety scale (DAS). DAS scores of 15–20 are considered as non-anxious. A non-anxious control group \( n = 18 \), nine males, nine females, undergoing extraction of one or more molars volunteered to undergo the procedure with conscious sedation. The characteristics of these two groups are shown in table 1.

No premedication was given. Articaine–epinephrine was administered for local anaesthesia when the procedure was expected to be painful. No other anaesthetic or analgesic drug was administered.

**Delivery system**

The TCI system was designed by one of the authors (F. E.). The program runs on a microcomputer connected to a Graseby 3400 infusion pump (Graseby Medical Ltd, Watford, UK) via an RS-232 serial interface. The computer program used a threecompartment mathematical model to calculate continuously the distribution of propofol. Pharmacokinetic microconstants derived by Gepts and colleagues \(^6\) (table 2) were incorporated into the computerized delivery system. The initial target concentration was entered into the computer before the start of sedation. The anaesthetist could manipulate the predicted concentration in any direction at any time. Induction of sedation was achieved by rapid infusion at a rate of 700 ml h\(^{-1}\) and thereafter the computer automatically delivered an infusion regimen that was calculated to maintain the target concentration constant. Predicted blood propofol concentrations, together with the propofol infusion rate, were stored on disk every 30 s. In addition, patient number, sex, age, ASA status and weight, together with details of the infusion profile, were stored within the disk file created by the TCI pump.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (mean (SD) [range] or number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Anxious patients</td>
</tr>
<tr>
<td>( n )</td>
<td>23</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>12/11</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30 [18–60]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacokinetic microconstants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Gepts and colleagues (^6)</td>
</tr>
<tr>
<td>Bias (%)</td>
<td>-37.6</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>37.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Sedation scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>( V_c : 241 ) (litre)</td>
</tr>
<tr>
<td>Anxious patients</td>
<td>( K_1 : 0.119 ) (min(^{-1}))</td>
</tr>
<tr>
<td>Cooperability/treatability</td>
<td>( K_1 : 0.114 ) (min(^{-1}))</td>
</tr>
<tr>
<td>( K_2 : 0.042 ) (min(^{-1}))</td>
<td>( K_2 : 0.0375 ) (min(^{-1}))</td>
</tr>
</tbody>
</table>

**Sedation procedure**

After obtaining baseline recordings of the electrocardiogram (ECG), heart rate (HR), non-invasive arterial pressure (NIAP) and oxygen saturation \( (SpO_2) \), a standardized conscious sedation regimen was initiated. An infusion of propofol with a preset target concentration of 2.5 \( \mu g \) ml\(^{-1}\) (study 1) was started until the patient had reached the desired clinical end-point of sedation. A five-point sedation scale was used (table 3). The aim was to reach and maintain sedation level 3. In addition, cooperation and treatability was an end-point in the anxious groups (table 3). If these clinical end-points were not reached within 3 min (inadequate sedation), the target concentration was increased, in steps of 0.2 \( \mu g \) ml\(^{-1}\), until treatment could be performed. When sedation level 3 was reached, the propofol target level was maintained, unless signs of over sedation became apparent (sedation level 4), as indicated by diminished response to communication or decreasing \( (SpO_2) \). In that event the target concentration was decreased in steps of 0.2 \( \mu g \) ml\(^{-1}\) and the dental procedure halted temporarily until the desired sedation level was regained. When a disinhibitory type of over sedation was present (agitation, excitement, restlessness and lack of cooperation), the target concentration was decreased in the same way. Oxygen supplementation was not administered routinely. When patients were sedated adequately, a second venous access site for blood sampling for measurement of propofol concentrations was established in a large forearm vein contralateral to the site of infusion.

At the end of the dental treatment, propofol infusion was discontinued and the patient allowed to recover in the dental chair. Recovery of cognitive and psychomotor function after sedation was tested by recall of personal data and the Romberg test. When responses to these tests had returned to pre-sedation values, the patient was allowed to go home under appropriate escort.
Monitoring

NIAP was measured automatically every 5 min using a Critikon Dinamap (1846 SX) arterial pressure monitor. Heart rate and \((S_{\	ext{PO}_2})\) were monitored continuously using a Criticon pulse oximeter. A standard single-channel ECG was displayed on a Hewlett-Packard ECG monitor (78345A). Data collection started before sedation and continued until 5 min after discontinuation of propofol infusion. The ECG monitor, arterial pressure monitor and pulse oximeter were interfaced to a personal computer which stored on disk heart rate, systolic, diastolic and mean arterial pressures, and \((S_{\	ext{PO}_2})\) at 30-s intervals, together with the time of recording. During the procedure, the dentist and anaesthetist continuously maintained verbal and non-verbal communication with the patient, and monitored the protective airway reflexes. The aim was to maintain sedation level 3 on the five-point sedation scale (table 3).

Venous blood sampling

Peripheral venous blood samples were obtained at the following times: 10 and 25 min after reaching the clinical end-point of sedation, and at 15-min intervals thereafter. A sample was also obtained 10 min after discontinuing propofol infusion. The sampling arm was maintained at body temperature with a blanket and placed horizontally without constricting bands. No tourniquet was used during sampling. Arterial pressure was measured on the sampling arm and measurements were not performed within the 5-min period before sampling. The deadspace fluid in the cannula was removed before each sampling. Serum samples were stored at 4°C until analysis within 30 days after collection. Propofol concentrations were assessed in duplicate by high performance liquid chromatography, as described by Plummer.8 Accuracy of the essay was 0.48% at 2.02 µg ml\(^{-1}\) and 1.46% at 4.04 µg ml\(^{-1}\). The lower limit of detection was 0.025 µg ml\(^{-1}\).

Computer analysis

Each measured blood concentration of propofol \((C_w)\) was compared with the corresponding delivery system predicted target concentrations \((C_p)\). In order to correct for the fact that the delivery performance of a TCI pump is never ideal,9,10 the simulated concentration \((C_{\text{sim}})\) was calculated on the basis of the delivery system record of the infusion profile actually administered to each individual (as opposed to that which should have been given).

The percentage prediction error, calculated for each datum point was defined as:

\[
\text{Prediction error (PE)} = \frac{C_{\text{sim}} - C_p}{C_p} \times 100 \quad (1)
\]

where \(C_p = \text{ith prediction of the plasma drug concentration in the ith patient, and } C_{\text{sim}} = \text{ith measurement of the plasma drug concentration in the ith patient.}

Bias is defined as the median prediction error11 and is a measure of the systemic tendency of the system to under or over estimate the measured concentration of blood propofol. If bias has a positive value, then the measured value is, on average, greater than the system prediction and vice versa.

\[
\text{Median prediction error (MDPE)} = \text{median } \{PE_i, j=1,...,N_i \} \quad (2)
\]

Precision is the median absolute performance error and is defined by:

\[
\text{(MDAPE)} = \text{median } \{|PE_i|, j=1,...,N_i\} \quad (3)
\]

where \(N_i = \text{number of performance errors obtained in the ith individual.}

Precision is a measure of the inaccuracy of the system.11 Corrected values for each of the above values were calculated in an analogous manner by substituting \(C_{\text{sim}}\) for \(C_w\). The ideal pharmacokinetic model for a delivery system produces minimum bias and precision values.11 In order to derive a new set of pharmacokinetic variables which would more accurately predict measured blood concentrations in anxious patients, drug input and measured propofol plasma concentration data were analysed by a program (pharmacokinetic optimization (PKOPT)) that uses non-linear regression to minimize the extended least-squares objective function (NONMEM objective function \((-2 \log \text{ likelihood} = -2LL))'.12,13 The program, developed by one of the authors (M. W.) was written in GFABasic for Windows (GFA Data Media (UK) Ltd) and runs in compiled form on an IBM 486 or a more powerful computer running either MS Windows 3.1/11 or Windows 95. Data input is highly automated and consists of the computerized record of each infusion profile generated by the TCI pump, together with a pre-formatted file containing the measured blood propofol data. The program is capable of analysing data either from individuals or from a population (population approach). It derives a set of new population pharmacokinetic variables which significantly (by chi-square testing \(P < 0.01\)) reduces the NONMEM objective function. The data obtained in study 1 were entered into the program, and a new set of microconstants was derived that should result in improved population bias and precision.

Clearance values of propofol for each individual in the study were calculated by obtaining the best fit to the measured propofol concentrations using the NONMEM objective function of the PKOPT program. The values thus obtained for the two patient groups were compared using the Mann–Whitney U test.

STUDY 2

The optimized kinetic dataset was tested prospectively in 12 highly anxious patients (five females, seven males) undergoing similar dental procedures. The target concentration was adjusted to obtain the same clinical end-point. To account for the anticipated reduced bias, the initial target concentration was set to 1.4 µg ml\(^{-1}\). In study 2, venous blood samples were obtained every 15 min after patients were
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Figure 1 Course of sedation in a representative anxious female patient (aged 34 yr, weight 59 kg). The figure depicts propofol concentration predicted by the pump algorithm (C_P), the corresponding calculation based on re-simulation of the actual drug delivery profile (C_sim) and measured serum propofol concentrations (C_m). The increases in infusion rates at 55 and 90 min are because of replacement of a near empty syringe with a replacement filled syringe. The propofol infusion rate is also indicated.

Figure 2 Propofol concentrations during conscious sedation in study 1 (anxious n = 23 and control n = 18) and study 2 (anxious n = 12) predicted by the pump algorithm (C_P), the corresponding calculation based on re-simulation of the actual drug delivery profile (C_sim) and measured serum propofol concentrations (C_m).

Sedation data are presented in table 4 and figure 2. The mean target concentration (C_T) necessary to maintain sedation level 3 in anxious patients was 2.6 (0.1) [range 2.3–3.1] µg ml⁻¹ (re-simulated values C_sim 2.4 (0.07) [range 2.1–2.8] µg ml⁻¹). Measured serum propofol concentrations (C_m) obtained between 20 and 35 min after the optimal sedation level was reached were 1.65 (0.2) [range 0.93–2.52] µg ml⁻¹ in anxious patients compared with 1.73 (0.3) [range 0.87–3.15] µg ml⁻¹ in the non-anxious control group. Mean duration of drug input was 63 [range 26–116] min. In the non-anxious control group, mean target concentration (C_T) at which satisfactory sedation was achieved was 2.4 (0.2) [range 1.3–2.7] µg ml⁻¹ (re-simulated values C_sim 2.12 (0.15) [range 1.15–2.45] µg ml⁻¹). Mean duration of infusion was 43 [25–94] min. Transient oversedation occurred in two patients in the anxious group and in three patients in the non-anxious control group.

Figure 3A shows the scatterplot of the percentage prediction errors compared with the corresponding simulated concentration for the two groups. The corrected median prediction error (bias) calculated for the anxious population was −32.4% compared with −22.2% in the non-anxious control group. Precision was 33.7% in the anxious population and 28.3% in the non-anxious control group. Therefore, in both groups the pump systematically overpredicted measured propofol concentrations. The time related course of prediction error for each individual in the

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Table 4 Sedation data (mean (sd) [range])

<table>
<thead>
<tr>
<th></th>
<th>Study 1 Anxious patients</th>
<th>Study 1 Non-anxious control patients</th>
<th>Study 2 Anxious patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infusion (min)</td>
<td>63 (23)</td>
<td>43 (17)</td>
<td>83 (37)</td>
</tr>
<tr>
<td></td>
<td>[26–116]</td>
<td>[25–94]</td>
<td>[56–188]</td>
</tr>
<tr>
<td>Preset target propofol concentration (C_p) (µg ml⁻¹)</td>
<td>2.63 (0.1)</td>
<td>2.4 (0.2)</td>
<td>1.63 (0.1)</td>
</tr>
<tr>
<td></td>
<td>[2.3–3.1]</td>
<td>[1.3–2.7]</td>
<td>[1.2–1.8]</td>
</tr>
<tr>
<td>Simulated blood propofol concentration (C_sim) (µg ml⁻¹)</td>
<td>2.39 (0.07)</td>
<td>2.12 (0.15)</td>
<td>1.36 (0.1)</td>
</tr>
<tr>
<td></td>
<td>[2.1–2.84]</td>
<td>[1.15–2.45]</td>
<td>[1.06–1.57]</td>
</tr>
<tr>
<td>Measured serum propofol concentration (C_m) (µg ml⁻¹) at 20–35 min during optimal sedation level</td>
<td>1.65 (0.2)</td>
<td>1.73 (0.3)</td>
<td>1.42 (0.27)</td>
</tr>
<tr>
<td></td>
<td>[0.93–2.52]</td>
<td>[0.87–3.15]</td>
<td>[0.45–2.07]</td>
</tr>
<tr>
<td>Dose rate (mg kg⁻¹ h⁻¹)</td>
<td>7.1 (0.8)</td>
<td>7.1 (1.0)</td>
<td>4.89 (1.7)</td>
</tr>
<tr>
<td></td>
<td>[5.9–8.7]</td>
<td>[4.5–8.7]</td>
<td>[6.3–6.7]</td>
</tr>
<tr>
<td>Total dose (mg h⁻¹)</td>
<td>513 (167)</td>
<td>490 (83)</td>
<td>410 (98)</td>
</tr>
<tr>
<td></td>
<td>[316–957]</td>
<td>[338–658]</td>
<td>[295–607]</td>
</tr>
<tr>
<td>No. of blood samples</td>
<td>5.7 (0.9)</td>
<td>4.5 (0.9)</td>
<td>5.7 (1.7)</td>
</tr>
<tr>
<td></td>
<td>[4–7]</td>
<td>[2–6]</td>
<td>[4–9]</td>
</tr>
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</table>
two groups is shown in figure 3B. There was no significant difference in propofol clearance between the two groups (fig. 4). Median clearance was 36.0 (11.9–62.1) ml kg$^{-1}$ min$^{-1}$ in anxious patients and 31.7 (13.9–50.5) ml kg$^{-1}$ min$^{-1}$ in non-anxious control subjects.

STUDY 2

The data obtained from the anxious group in study 1 were entered into the PKOPT program and a new set of population microconstants (table 2) was derived which significantly minimized ($P < 0.01$) the NONMEM objective function for the experimental data from study 1 and which should result in improved pump performance. For each measurement of blood propofol a new prediction error was calculated on the basis of a new predicted value based on the new pharmacokinetic model derived by the computer program. The values of bias and precision calculated on the basis of the new optimized model were 0.02 and 25%, respectively (fig. 5a) The NONMEM objective function ($-2LL$) was reduced from 317 to 195. No additional improvement in the objective function was obtained by an additional regression step to include patient age.

The refined microconstants were then used to update the TCI pump delivery program and both the clinical and pharmacokinetic performance of this system were assessed prospectively in a second group of 12 patients. The clinical data are shown in table 4. No oversedation was encountered with the modified pharmacokinetic settings in any patient. The target propofol concentration in study 2 necessary to maintain sedation level 3 was 1.6 (0.1) [range 1.1–1.9] g ml$^{-1}$ (re-simulated values 1.36 [range 1.06–1.57] g ml$^{-1}$) (fig. 2). Mean duration of propofol delivery was 83 (37) [range 56–188] min. Measured serum propofol concentration obtained between 20 and 35 min after reaching the optimal sedation level was 1.42 (0.27) g ml$^{-1}$. The time course of pump predictive performance is shown in figure 5b. Median prediction error (bias) after re-simulation was $5.0\%$ and precision was 16%. Bias and precision with the optimized kinetic set were significantly ($P < 0.01$) less than the values obtained in study 1. A mean of 2 (range 0–3) alterations in target concentrations were made in all patients.

In all patients, haemodynamic and ($S_{O_2}$), indices were stable and there were no instances of deviation greater than 15% from baseline.

Discussion

In study 1, the measured serum propofol concentration necessary to maintain the optimal level of sedation in our study was approximately 1.5 g ml$^{-1}$, and
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There were no significant differences between anxious and non-anxious control patients. In study 2, similar serum propofol concentrations were measured in anxious patients using the optimized kinetic data set, despite lower target concentrations being set on the modified TCI system. The results of study 1 revealed no evidence to support the existence of a difference in propofol clearance between anxious patients and non-anxious controls.

For study 1, in both anxious and non-anxious subjects receiving subanaesthetic doses of propofol via a target-controlled infusion system using Gepts' kinetic dataset, measured values of propofol were systematically overestimated by the delivery system model. The clinical setting in which Gepts' microconstants were derived differed considerably from the conditions in our study involving dental outpatients, and these differences may partly explain the large negative bias observed in our study. Gepts' parameter set was derived from three groups of six patients who were older than the dental patients and volunteer subjects in our study. Propofol was administered as a constant rate infusion for at least 2 h at a rate of 3 μg ml⁻¹ h⁻¹ in patients aged approximately 60 yr, 6 μg ml⁻¹ h⁻¹ in patients aged 50 yr and 9 μg ml⁻¹ h⁻¹ in patients aged 40 yr, who underwent urological procedures under spinal or local anaesthesia. The infusion rates necessary to maintain conscious sedation in our dental patients and volunteers were of the order of 4.5–8.7 μg ml⁻¹ h⁻¹. Lastly, in Gepts' analysis, arterial sampling was performed, whole blood samples were collected and whole blood propofol concentrations were determined whereas in our study, sampling was from a venous site and serum propofol concentrations were measured.

We opted to obtain venous samples to minimize discomfort and risk in our highly anxious patients. The decision to use venous rather than arterial blood samples may have resulted in lower measured blood propofol concentrations compared with Gepts' study. During a bolus and infusion regimen that achieves and maintains a constant arterial concentration, it may be expected that the AV differences are greatest initially as drug is distributed rapidly into the tissues. This difference diminishes as the tissues become saturated, until after some minutes arterial and venous concentrations are the same. Chiou demonstrated that at steady state during constant infusion, there was no difference in arterial and venous blood (plasma) concentrations during the dosing interval as peripheral tissue uptake of propofol is zero. Coetzee and colleagues suggested that in evaluating propofol TCI, it is preferable to use arterial concentrations, but venous concentrations can be used too, bearing in mind that propofol venous concentrations are lower than arterial values and that sampling should be performed several minutes after adjustment to the targeted concentration. Because we obtained venous blood 10 min after reaching the clinical end-point of sedation (at least 15 min after the start of infusion), it is unlikely that the difference between arterial and venous blood propofol concentrations was sufficient to explain the observed negative bias. We have determined propofol concentrations in serum. Propofol concentrations in whole blood, plasma or serum may differ. Coetzee and colleagues compared propofol concentrations in whole blood, plasma and serum in 65 samples obtained from 10 patients, with propofol concentrations in the range 0.5–7.5 μg ml⁻¹. Propofol concentrations in whole

Figure 5  A: Percentage prediction error (PE%) vs predicted propofol concentration ($C_{sim}$) based on re-simulation using the actual amount of propofol delivered and the optimized pharmacokinetic microconstants derived with PKOPT program in anxious patients from study 1 and anxious patients in the prospective study 2. B: Percentage prediction error (PE%) vs time for each individual, using the optimized pharmacokinetic microconstants derived with the PKOPT program in anxious patients from study 1 and anxious patients in the prospective study 2.
blood were, on average, 0.3 \( \mu g \) ml\(^{-1} \) higher than in serum, and there were no significant differences between concentrations in plasma and serum. The authors concluded that the differences were not large enough to influence the concentrations achieved and the prediction errors. It is possible that part of the observed difference between predicted and measured propofol concentration in our study can be attributed to the difference in blood propofol determination between our study and that of Gepts' (whole blood).

In both the anxious and non-anxious groups in our study, over prediction of the delivery system model (Gepts) diminished with time such that after approximately 60 min of infusion time the model tended rather to under predict the measured concentrations than vice versa. This observation suggests that, in the context of the present study, the use of the Gepts' model in the delivery system produced an inherent tendency to drift towards a deeper level of sedation despite the pump settings remaining constant. The reason for this is apparent from figure 6. This illustrates the results of a computer simulation of predicted propofol concentrations in one of the study patients receiving propofol from the TCI system programmed with Gepts’ kinetic set, but projected instead into the new model derived by the optimization program. It can be seen that the predicted propofol concentrations according to the new model are initially substantially lower than those predicted by the Gepts’ model but progressively increase during the course of the infusion. The refined model derived by the optimization program successfully eliminated this problem and produced a stable time relationship between measured and predicted values.

Hepatic extraction of propofol is high and clearance is dependent on liver blood flow. Propofol has been shown to decrease cardiac output in a dose-dependent manner in humans, which in turn may dynamically influence propofol kinetics by reducing the rate of distribution to peripheral tissues and thereby contributing to a reduction in hepatic blood flow. It is conceivable that the higher age of Gepts’ patients, possibly combined with reduction in cardiac output or hepatic blood flow, or both, may have resulted in lower values for propofol clearance than those observed in our study. The substantial negative bias observed in our sedation study was predicted by Coetzee and colleagues who proposed that the clearance of propofol is concentration dependent. Clearance and distribution of the drug were postulated to occur at a faster rate at lower concentrations. Thus a pharmacokinetic study performed at higher concentrations would produce slower kinetics than one performed at a lower concentration. The results of our study support the hypothesis that the pharmacokinetics of propofol are concentration dependent.

Skipsey and colleagues reported in a study involving older patients undergoing orthopaedic procedures under regional anaesthesia that their patients were satisfactorily sedated at a mean blood propofol concentration of 1.05 [range 0.15–2.63] \( \mu g \) ml\(^{-1} \). Our findings are in accordance with their statement that patients with a blood propofol concentration of approximately 1–1.5 \( \mu g \) ml\(^{-1} \) are sedated but respond to verbal stimulation. This appeared to be true both in anxious patients and non-anxious control subjects.

The main purpose of a TCI pump is to produce a stable blood concentration of the delivered drug which is as close as possible to that predicted by the delivery system algorithm. The pharmacokinetic performance of any TCI system is thus highly dependent on how well the applied pharmacokinetic data in the delivery program match the characteristics of the target population. Inter- and intra-patient variability, variable intraoperative haemodynamic states and changing surgical stimulus contribute to considerable variability in pump performance in clinical practice. In the context of conscious sedation, the appropriateness of the pharmacokinetic delivery system model is particularly important because the therapeutic range for sedation is much smaller than for general anaesthesia. Our study demonstrated that the 10–90 percentile range predicted target concentration selected for conscious sedation in anxious patients was 2.11–2.65 \( \mu g \) ml\(^{-1} \) whereas the corresponding range for general anaesthesia is 2–10 \( \mu g \) ml\(^{-1} \). Relatively small prediction errors result in over or under sedation.

One of the main objectives of this study was to derive a new set of pharmacokinetic constants which more accurately described the elimination of propofol in anxious patients undergoing conscious sedation. The optimized model produced significantly \((P<0.01)\) improved pharmacokinetic performance compared with the original system using the pharmacokinetic microconstants derived by Gepts and colleagues and this result could be confirmed in a prospective study. The new model also demonstrated improved time related performance producing accurate and stable concentrations of propofol over a time period of up to 2 h.

**Acknowledgments**

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References


