Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion

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Differences in the pharmacokinetics of propofol between male and female patients during and after continuous infusion have not been described in detail in patients aged 65 yr and older. To increase our insight into the pharmacokinetics of propofol in this patient population and to obtain pharmacokinetic parameters applicable in target controlled infusion (TCI), the pharmacokinetics of propofol during and after continuous infusion were studied in 31 ASA class 1 and 2 patients, aged 65–91 yr, scheduled for general surgery. Patients received propofol 1.5 mg kg^{-1} i.v. in 1 min followed by 7 mg kg^{-1} h^{-1} until skin closure in the presence of a variable rate infusion of alfentanil during oxygen–air ventilation. On the basis of arterial blood samples that were taken up to 24 h post-infusion, the pharmacokinetics of propofol were evaluated in a two-stage manner. Multiple linear regression analysis was used to explore the effect of age, weight, gender and lean body mass as covariates. Gender significantly affected the pharmacokinetics of propofol. V_3, Cl_1 and Cl_2 were significantly different between male and female patients, weight only affected Cl_1. The pharmacokinetic parameters were: V_1=4.88 litre, V_2=24.50 litre, V_3 (litre)=115+147×gender (gender: male=1, female=2), Cl_1 (litre min^{-1})=–0.29+0.022× weight+0.22×gender, Cl_2 (litre min^{-1})=2.84–0.65×gender (male=1, female=2), and Cl_3=0.788 litre min^{-1}.

Ageing is accompanied by all types of physiological changes and age-related diseases that have implications for the provision of general anaesthesia. Besides changes in the pharmacodynamics of anaesthetic agents that occur with increasing age, age-related changes in body composition, tissue drug binding and tissue perfusion may affect the distribution, redistribution and elimination of anaesthetic agents. These changes may be different between male and female patients.

As the elderly population increases, elderly patients are scheduled for general surgery with increasing frequency. However, rational dosing schemes for propofol in this population are not available. So far, three studies[1–3] have described the pharmacokinetics of propofol during continuous infusion in the elderly. One manuscript described the pharmacokinetics of propofol solely in male patients.[1] The second study determined the pharmacokinetics of propofol in a non-clinical environment in volunteers with only few elderly involved.[2] Lastly, Schüttler and colleagues recently described a population pharmacokinetic parameter set for propofol.[3] However, the small number of elderly patients in this population (10%), the propofol dosing regimen in these patients (some only received a bolus dose), and the short period of time during which concentration–time data of these patients were collected (on average 55 min) leads us to believe that this population pharmacokinetic data set may be less suitable for application in continuous infusion techniques in elderly patients. As propofol is increasingly administered in elderly patients either by manual or target controlled infusion, we studied the pharmacokinetics of propofol in male and female elderly patients during and after termination of a continuous infusion when given as a component of total i.v. anaesthesia for general surgery.

Subjects and methods

With approval of the local Medical Ethics Committee and after obtaining informed consent, 32 patients, ASA I or II,

aged 65 yr or older (range 65–91 yr), scheduled for general surgery were studied. Patients with known cardiac, pulmonary or renal disease were excluded as were patients consuming more than 20 g of alcohol or smoking more than 10 cigarettes per day.

Patients received temazepam 10 mg orally, 1 h pre-operatively. In the operating room, an i.v. cannula was inserted into a large forearm vein for infusion of propofol and alfentanil and a cannula was inserted into a radial artery for the continuous measurement of arterial blood pressure and the collection of blood samples for determination of blood propofol concentrations. The ECG, arterial blood pressure, heart rate, end-tidal carbon dioxide partial pressure and oxyhaemoglobin saturation (Sp_{O_2}, Nellcor N-200, Hayward, CA) were monitored continuously throughout the study.

Before induction of anaesthesia, patients received 500 ml of a colloid solution (Gelofusine). With the patients breathing 100% oxygen, anaesthesia was induced by a manually controlled infusion (Beckton Dickinson, Brézins, France) with a bolus dose of propofol of 1.5 mg kg^{-1} over 1 min followed by a continuous infusion of 7 mg kg^{-1} h^{-1} that was maintained constant until skin closure. When consciousness was lost, vecuronium, 0.1 mg kg^{-1}, was given i.v. and the trachea intubated. The lungs of the patients were then ventilated with oxygen in air (1:2) and ventilation adjusted to maintain the end-tidal carbon dioxide partial pressure between 4–4.5 kPa. In addition, patients received a continuous infusion of alfentanil of 0–50 μg kg^{-1} h^{-1} i.v. that was varied according to the presence or absence of patient responses, and terminated 10 min before skin closure. No response was defined as a systolic blood pressure within a 15% range of the preoperative mean, a heart rate of less than 90 beats min^{-1} in the absence of hypovolaemia, absence of autonomic responses and no movement to surgical stimuli. Post-operative pain relief was provided with rectal paracetamol up to 3 g per 24 h and i.m. methadone up to 0.15 mg kg^{-1} four times daily. Twenty-four hours post-operatively the patients were asked for any recall of events during the study period.

Arterial blood samples of 3 ml for the determination of whole blood propofol concentration were taken at 1, 3, 5, 10, 15, 20, 25, 30 min and then every 15 min after the start of the infusion of propofol, and at 0.5, 1, 2, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 120, 180, 240, 360, 720, 1080 and 1440 min after the termination of the infusion of propofol. The blood samples were transferred into test tubes containing potassium oxalate and stored at 4°C. Propofol concentrations in blood were measured within 12 weeks by reversed-phase high-performance liquid chromatography (HPLC).[4] The detection limit was approximately propofol 40 ng ml^{-1} blood. The coefficient of variation of the HPLC method did not exceed 10% in the concentration range encountered in this study.

The pharmacokinetics of propofol were determined in each patient by fitting two and three compartment models to the concentration–time data with a weighted ($1/y^2$) least squares non-linear regression analysis (software package WinNonLin, Scientific Consulting, Inc., Cary, NC, USA). In a two-stage manner, the simple average pharmacokinetic parameter set was determined. The effect of age, gender, total body weight and lean body mass on the pharmacokinetic parameters was then evaluated by univariate and multivariate linear regression analysis (SPSS 9.0, SPSS Inc USA). Based upon partial F-tests ($P<0.05$), successive variables were included. Finally, if more than one covariate was included plausible interaction terms were examined and based upon F-tests ($P<0.05$) this term was either included or excluded. Independent covariates were tested for multicollinearity. If the tolerance exceeded 0.5 multicollinearity was considered to be not substantial. The simple (average) model and the final (complex) pharmacokinetic parameter set were retrospectively tested for their clinical value by determining the accuracy with which the parameters predicted the measured blood propofol concentrations in the individual patients.

The performance error (PE) was calculated as:

$$PE = \frac{C_m C_p}{C_p} \times 100,$$

where C_m and C_p are the measured and predicted blood propofol concentrations. Subsequently, the bias and inaccuracy associated with each pharmacokinetic parameter set were assessed by determining the median performance error (MDPE), the median absolute performance error (MDAPE), and the corresponding interquartile ranges (25–75%).

Data are presented as mean (SD), median and range, or percentage, unless stated otherwise. $P<0.05$ was considered as the minimum level of statistical significance.

Results

The concentration–time data of 31 (16 male, 15 female) of the 32 patients that were enrolled in the study were available for evaluation. In one patient, the infusion of propofol was interrupted because of an obstruction of the i.v.-line and the concentration–time data of this patient were not included in the evaluation. No significant differences existed between the male and female patients with respect to age (mean (SD)) (73.3 (6.1) vs 72.5 (6.2) yr), weight (75.3 (9.5) vs 71.1 (11.1) kg), propofol infusion duration (120.1 (79.8) vs 111.0 (44.9) min) or mean alfentanil infusion rate (37.2 (28.2) vs 50.4 (21.5) μg kg^{-1} h^{-1}). Surgical procedures included herniotomies, mastectomies, cholecystectomies and minor bowel surgery.

From the 31 patients, a total of 932 blood samples for determination of blood propofol concentrations were taken over a 24 h period. The pharmacokinetics of propofol were

Table 1 The simple (average) and complex (final) pharmacokinetic parameter set (SD) of propofol in the elderly. M, mass (kg); G, gender (male=1, female=2)

	Simple (average) pharmacokinetic parameter set	Complex (final) pharmacokinetic parameter set	R^2	P
V_1 (litre)	4.88 (2.23)	4.88 (2.23)		
V_2 (litre)	24.5 (12.1)	24.5 (12.1)		
V_3 (litre)	334 (197)	115+147*G	0.144	0.035
Cl_1 (litre min^{-1})	1.65 (0.37)	–0.29+0.022 * M+0.22 * G	0.477	0.001
Cl_2 (litre min^{-1})	1.88 (0.83)	2.84–0.65*G	0.155	0.028
Cl_3 (litre min^{-1})	0.788 (0.256)	0.788 (0.256)		

Table 2 The accuracy (median performance error; MDPE) and precision (median absolute performance error; MDAPE) and interquartile ranges of the measured versus predicted propofol concentrations on the basis of the complex pharmacokinetic parameter set of this study and on the basis of those predicted with the use of the pharmacokinetic parameter sets by Dyck and Shafer,[1] Schnider and colleagues[2] and Schüttler and colleagues[3]

	MDPE (25–75%)	MDAPE (25–75%)
This study	1 (–5 to 13%)	18 (14–22%)
Dyck and Shafer[1]	18 (–5 to 26%)	33 (29–37%)
Schnider and colleagues[2]	20 (9–33%)	27 (20–35%)
Schüttler and colleagues[3]	–38 (–53 to –29%)	40 (32–53%)

best described on the basis of a three-compartment model in all patients. Gender significantly affected the pharmacokinetics of propofol. V_3, Cl_1 and Cl_2 were significantly different between male and female patients. In addition, Cl_1 was weight dependent. The simple and final complex pharmacokinetic parameter sets are described in Table 1. The performance of the simple average pharmacokinetic parameter set, as tested retrospectively by computer simulation in the individual patients, showed a reasonable performance (MDPE (25–75%), 2% (–9 to 15%); MDAPE 22% (18–26%)). The addition of the covariates improved the performance as shown by a reduction in both the bias and inaccuracy and their interquartal ranges (MDPE (25–75%), 1% (–5 to 13%); MDAPE 18% (14–22%), Table 2). For the application of the pharmacokinetic parameter set to a target controlled infusion, the performance of the final complex model was determined as well only for the period of propofol infusion: (MDPE (25–75%), 3% (–2 to 13%); MDAPE 14% (11–20%)). The performance of the complex model is illustrated in Fig. 1, which shows the measured and predicted concentration-time data in the patients with the best and worst performances as based on MDPE.

Discussion

Based on empirical findings, the propofol dosage and rate of administration in the elderly generally are reduced to diminish unwanted side effects. To what degree the dosage should be reduced and if gender affects this reduction, however, is not known. This report describes the concentration–time relationship of propofol in elderly female and male patients during and after propofol administration by a standard manually controlled infusion in the presence of a variable-rate infusion of alfentanil during total i.v. anaesthesia for general surgery.

Gender differences in the elderly receiving propofol

In this study, we found that gender affected the pharmacokinetics of propofol in elderly patients. The pharmacokinetic analysis revealed a larger slow peripheral volume of distribution (V_3), a higher metabolic (Cl_1) but a reduced rapid peripheral clearance (Cl_2) in elderly female patients compared with elderly male patients. Previously, Dyck and Shafer[1] only studied male patients, Schüttler and Ihmsen[3] did not find a gender difference in the propofol pharmacokinetics, whereas Schnider and colleagues[2] described that gender of itself did not affect the pharmacokinetics of propofol but, by affecting lean body mass (LBM), influenced the metabolic clearance. The LBM of for instance a 73-yr-old, 75 kg, 180 cm male is 60.2 kg, whereas a female with the same characteristics has a LBM of 54.6 kg. As a consequence, according to Schnider and colleagues[2] the clearance in this elderly male is 1.80 litre min^{-1} compared with 2.18 litre min^{-1} in the elderly female. When elderly male and female patients are given the same propofol infusion scheme the blood propofol concentrations in the female patients will be approximately 10% lower compared to that in the male. These results are based on both the pharmacokinetics of Schnider and colleagues[2] and on the pharmacokinetics reported in this study (Fig. 2). The gender related differences may be explained on the basis of gender related differences in physiological parameters such as cardiac output and amount of body fat. Male patients generally exhibit a higher cardiac output and thus a greater hepatic perfusion compared with females.[6] For a high extraction-ratio drug like propofol, hepatic clearance is strongly correlated to hepatic perfusion and a gender related difference in hepatic perfusion may explain the difference in clearance found in this study. Similarly, the difference in the amount of body fat between elderly male and female patients may be responsible for the greater peripheral slow volume of distribution (V_3) in female compared with male patients in our study. Clinically, these results indicate that in order to assure the same blood propofol concentration in elderly female and male patients, female patients require an approximately 10% higher propofol infusion rate. Furthermore, when female and male patients receive the same infusion scheme, the lower blood propofol concentrations in female patients (Fig. 2) may explain the described difference in speed of recovery between female and male patients.[7] When female patients experience lower blood propofol concentrations compared with male patients during similar propofol infusion schemes, in the presence of a similar pharmacodynamic profile, female patients will regain consciousness more rapidly than male patients.
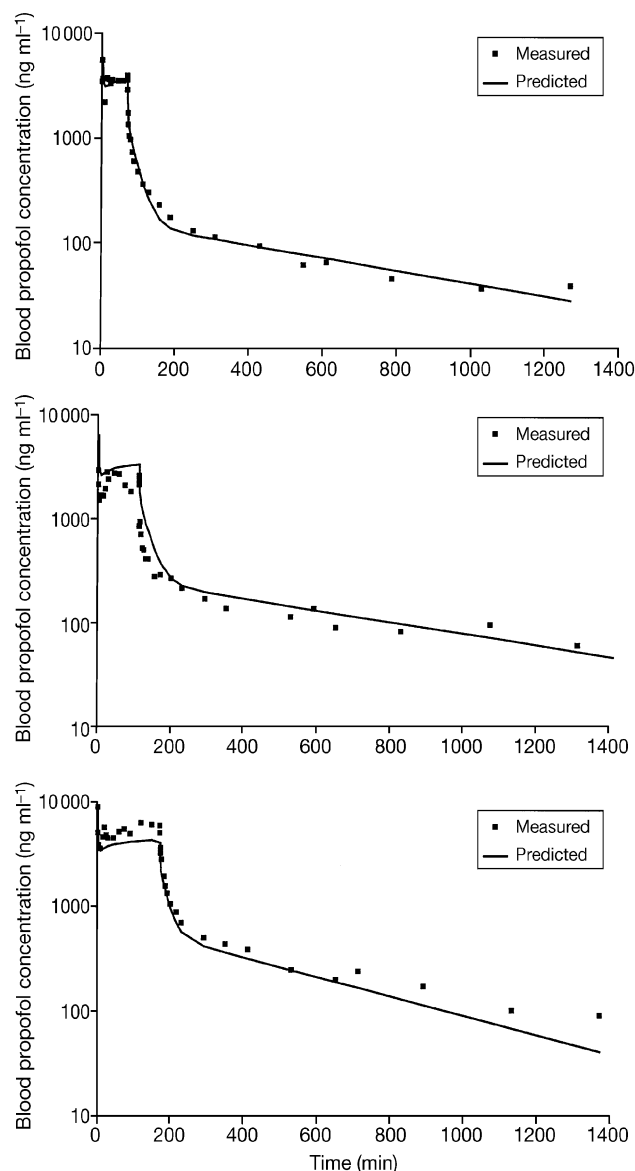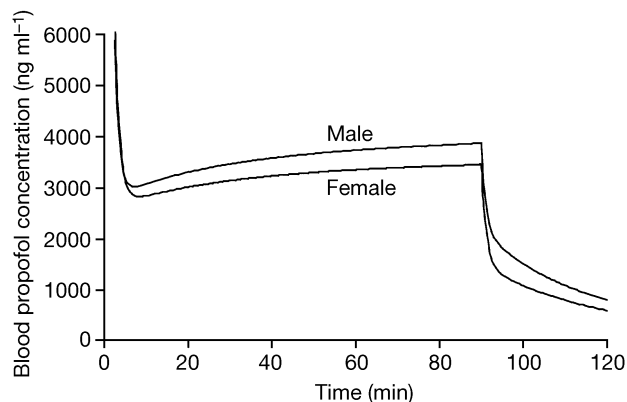
Fig 2 Predicted concentration-time relationship in an elderly female and male patient (both aged 73 yr, weighing 75 kg and being 180 cm tall) who receive a propofol bolus dose of 1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} for 89 min. Based on the complex pharmacokinetic model of this study, the predicted propofol concentrations during continuous infusion of propofol are 10–15% higher in male compared to female patients receiving the same infusion scheme.
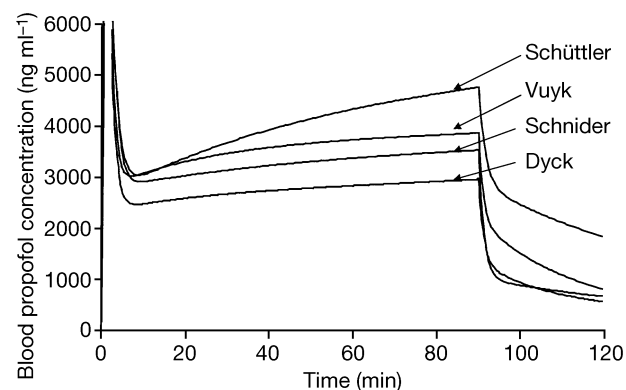

Fig 3 Predicted concentration-time relationship in an elderly male patient (aged 73 yr, weighing 75 kg and being 180 cm tall) who receives a propofol bolus dose of 1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} for 89 min as based on the pharmacokinetic parameter sets determined by Dyck and Shafer,[1] Schnider and colleagues,[2] Schüttler and colleagues[3] and in this study. Compared with the predicted propofol concentrations based on the pharmacokinetic model of this study, the pharmacokinetics by Schüttler and colleagues[3] result in concentrations that are 20% higher, in contrast to those based on the pharmacokinetic parameter sets by Schnider and colleagues[2] and Dyck and Shafer[1] that result in concentrations that are 5 and 15% lower.

Fig 1 Measured and predicted propofol concentrations based on the complex pharmacokinetic model in the patient with the best predicted propofol concentrations (upper panel; MDPE (interquartile range) 0% (−11 to 10%) and MDAPE 11% (5–26%)) and in two patients with the most overpredicted (middle panel: MDPE −26% (−45 to −5%) and MDAP 32% (14–47%)) and underpredicted propofol concentrations (lower panel: MDPE 32% (1–47%) and MDAPE 32% (12–49%)).

Gender differences in relation to other i.v. anaesthetics

The female patients in this study exhibited a larger slow peripheral volume of distribution (V_3), a higher metabolic (Cl_1) but reduced rapid peripheral clearance (Cl_2) compared with male patients. With respect to other i.v. hypnotic agents, the gender related changes in the pharmacokinetics of propofol closely correspond to those of midazolam described by Greenblatt.[8] The clearance of midazolam is lower and the volume of distribution is larger in female compared with male patients. In contrast, with thiopental,

gender has no effect on the pharmacokinetics.[9] Similarly, for the opioids remifentanil and sufentanil the pharmacokinetics are unchanged between male and female patients.[10 11] Of the opioids, only alfentanil exhibited a gender effect on the pharmacokinetics; the central compartment was 15% larger in female compared with male patients in a study by Maitre and colleagues.[12]

Computer simulation of propofol pharmacokinetics in the elderly

The clinical consequences of the pharmacokinetics of propofol observed in this study were compared with those
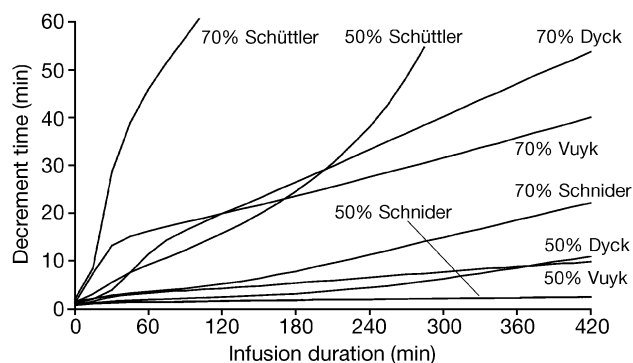
Fig 4 Fifty per cent and 70% decrement times (DT) *vs* infusion duration, based on the pharmacokinetic parameter sets determined by Dyck and Shafer,[1] Schnider and colleagues,[2] Schüttler and Ihmsen[3] and in this study. Fifty per cent and 70% decrement times are defined as the times required for the propofol concentration to drop by 50 or 70% after termination of a target controlled infusion that had been given with a constant target concentration for a given infusion duration.

based on the three parameter sets thus far described in the elderly[1-3] using a computer simulation of an infusion scheme as used in this study (1.5 mg kg^{-1} in 1 min followed by 7 mg kg^{-1} h^{-1} thereafter, Fig. 3). The measures of performance of these three other parameter sets in relation to those determined in this study were determined (Table 2). The computer simulations reveal that, based on the pharmacokinetics described in this manuscript, the predicted blood propofol concentrations are somewhat higher than those based on the pharmacokinetic data reported by Dyck and Shafer[1] and Schnider and colleages.[2] This may be the result of the fact that in contrast to the patients of Dyck and Shafer[1] and Schnider and colleages,[2] our patients were studied in a clinical setting and received alfentanil in addition to propofol. Recently, alfentanil has been shown to affect the pharmacokinetics of propofol such that in the presence of alfentanil propofol concentrations are increased by about 18%.[5] In that study, alfentanil reduced both the volume of distribution and the clearance of propofol. The mechanism of this interaction remains yet unknown.

In contrast to the data reported by Dyck and Shafer[1] and Schnider and colleagues,[2] the recently described population pharmacokinetic parameter set by Schüttler and Ihmsen[3] correlates much less with our data (Table 2, Fig. 3). Schüttler and Ihmsen[3] evaluated propofol concentration-time data from a heterogeneous data set. Compared with the previously described data sets[1 2] and the data reported in this study, the central compartment is larger and the clearance much smaller in the data set described by Schüttler and Ihmsen.[3] Consequently, 50 and 70% decrement times in the elderly calculated from the data of Schüttler and Ihmsen are very different from those calculated from the other studies (Fig. 4). Compared with our data and those by Dyck and Shafer[1] and Schnider and colleagues[2] the predicted propofol concentrations during propofol infusion based on the data of Schüttler are significantly higher (Fig. 3). Whereas according to our pharmacokinetic parameter set and those of Dyck

and Shafer[1] and Schnider and Ihmsen[2] the propofol concentration during constant-rate infusion remains stable after approximately 90 min of infusion. The propofol concentrations continue to increase according to the pharmacokinetic parameter set by Schüttler and Ihmsen[3] resulting in 60–70% higher predicted concentrations after a 6 h infusion. What may be the cause of this discrepancy? Of the 270 patients studied by Schüttler and colleagues[3] only a small minority was aged 65 yr or older (approximately 10%) in contrast to for instance a large group of patients aged 11 yr or younger (approximately 35%). Furthermore, from the three groups of patients that contained elderly patients (groups 3, 5 and 7) the patients from group 5 only received a bolus dose of propofol. Clearly, evaluation of the concentration–time data from these patients will be less useful for application in a continuous infusion setting such as TCI. From the remaining elderly patients (groups 3 and 7) concentration–time data were only gathered for a mean period of 55 min. From these data taken over such a short period, it is difficult, if not impossible, to accurately estimate the metabolic clearance and/or slow distribution clearance of propofol. Methodological issues, thus, have led to a population pharmacokinetic parameter set that, in elderly patients, is considerably different from the pharmacokinetic parameter set presented in this manuscript and those described by Dyck and Shafer[1] and Schnider and colleagues.[2] Consequently, when applied in TCI the Schüttler pharmacokinetic parameter set will result in propofol concentrations that will be significantly lower than the desired target concentration and will decrease with increasing infusion duration.

The use of the Diprifusor® in the elderly

Many anaesthetists use the Diprifusor® (Zeneca Pharma, Macclesfield, UK) for target controlled infusion in elderly patients, although the pharmacokinetic parameter set incorporated has not included age or gender as covariates. We therefore evaluated the performance of the Marsh pharmacokinetic parameter set,[13] included in the Diprifusor®, in elderly patients. Figure 5 shows in the upper panel the infusion rates given to reach and maintain a target propofol concentration of 3 µg ml^{-1} by the Diprifusor® and by a TCI device provided with the pharmacokinetics determined in this study in an elderly male patient. As the Diprifusor® does not correct for the smaller V_1 and reduced clearance in the elderly,[2] during TCI the Diprifusor® will administer an unnecessary high infusion rate to maintain any desired target concentration in the elderly. The lower panel of this figure shows the estimated blood propofol concentrations using the pharmacokinetic parameter set determined in this study when provided with the infusion rate-time data required to reach and maintain a target propofol concentration of 3 µg ml^{-1} on the basis of the pharmacokinetic parameter set included in the Diprifusor®.[13] Figure 5 shows that using the Diprifusor® for TCI in the elderly will result
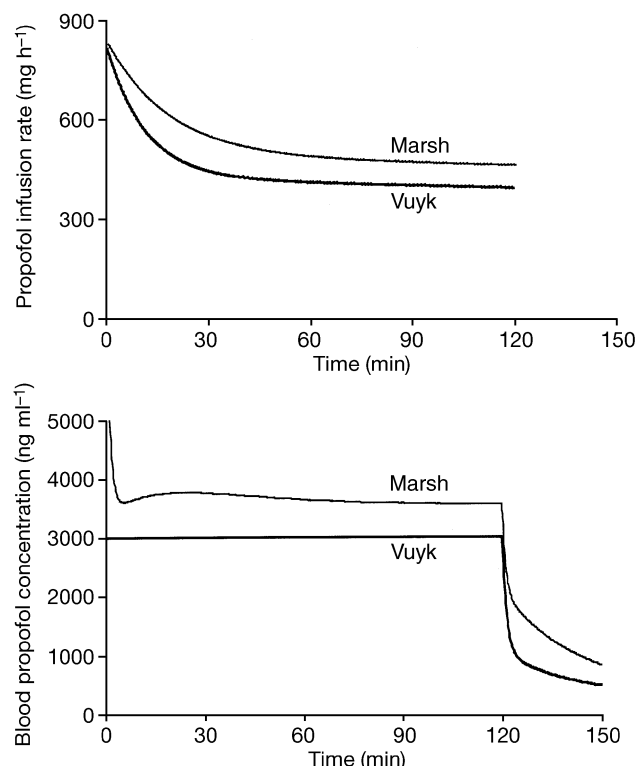
Fig 5 (Top panel) The infusion rates required to reach and maintain a target propofol concentration of 3 μg ml^{-1} for 120 min in an elderly male patient (aged 73 yr weighing 75 kg and 180 cm tall) as based on the pharmacokinetic parameter sets of this study and those used in the Diprifusior® by Marsh and colleagues.[13] (Bottom panel) The blood propofol concentrations as predicted by computer simulation using the pharmacokinetic parameter set of this study in an elderly male patient (aged 73 yr, weighing 75 kg and 180 cm tall) when provided with the infusion rate-time data required to reach and maintain a target propofol concentration of 3 μg ml^{-1} on the basis of pharmacokinetics incorporated in the Diprifusior® by Marsh and colleagues.[13]

patients resulting in lower concentrations in elderly female patients compared to elderly male patients given the same infusion scheme. Consequently, elderly female patients should be given approximately 10% higher infusion rates compared with elderly male patients to assure the same blood propofol concentration is reached.

in blood propofol concentrations that are approximately 20–30% higher than the targeted. Again based on our data this discrepancy will be 10% smaller in female compared to male patients. Consequently, on pharmacokinetic grounds the target concentration in elderly patients should be reduced equivalently to assure a similar effect as in younger patients. Age related pharmacodynamic changes[14] will require an even further reduction in target concentration with increasing age to assure a stable effect of propofol in patients of all ages.

We defined the pharmacokinetics of propofol when given by continuous infusion in female and male patients aged 65–91 yr in a clinical setting in the presence of alfentanil. Gender affects the pharmacokinetics of propofol in elderly

References

1 Dyck JB, Shafer SL. Effect of age on propofol pharmacokinetics. *Sem Anaesth* 1992; **XI** (Suppl 1); 2–4

2 Schnider TW, Minto CF, Gambus PL, *et al.* The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170–82

3 Schüttler J, Ihmsen H. Population pharmacokinetics of propofol. *Anesthesiology* 2000; **92**: 727–38

4 Kuiper JA, Boer F, Olieman W, Burm AGL, Bovill JG. First-pass lung uptake and pulmonary clearance of propofol. Assessment with a recirculatory indocyanine green model. *Anesthesiology* 1999; **91**: 1780–7

5 Vuyk J, Mertens MJ, Vletter AA, Burm AGL, Bovill JG. Alfentanil modifies the pharmacokinetics of propofol in volunteers. *Anesthesiology* 1997; **87** (Suppl): A300

6 Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 1998; **275**: 1909–20

7 Gan TJ, Glass PS, Sigl J, Sebel P, Payne F, Rosow C, Embree P. Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *Anesthesiology* 1999; **90**: 1283–7

8 Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI. Effect of age, gender and obesity on midazolam kinetics. *Anesthesiology* 1984; **61**: 27–35

9 Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. *Anesthesiology* 1990; **72**: 412–22

10 Minto CF, Schnider TW, Egan TD, *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10–23.

11 Gepts E, Shafer SL, Camu F, *et al.* Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology* 1995; **83**: 1194–204

12 Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR. Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; **66**: 3–12

13 Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; **67**: 41–48

14 Schnider TW, Minto CF, Shafer SL, *et al.* The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502–16