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Clinical Investigation

Pharmacokinetic Model Selection for Target Controlled Infusions of Propofol: Assessment of Three Parameter Sets

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Abstract

Background: Computer-assisted target controlled infusions (TCI) result in prediction errors that are influenced by pharmacokinetic variability among and within patients. it is uncertain whether the selection of a propofol pharmacokinetic parameter set significantly influences drug concentrations and clinical acceptability.

Cited Here...: Thirty patients received similar propofol TCI regimens after being randomly allocated to one of three parameter sets. Arterial and venous concentrations were measured and prediction errors calculated from pooled and intrasubject data.

Cited Here...: Arterial propofol concentrations in the Dyck group revealed greater bias (mean 43%) than did those in the Marsh (-1%) and Tackley (-3%) groups. The Dyck group also showed greater inaccuracy (mean:47%) than the Marsh (29%) and Tackley (24%) groups. There was little tendency for measured concentrations to vary from targeted values over time (divergence). Variability about an observed mean in individual patients (wobble) was low. Venous propofol concentrations were initially much less than arterial concentrations, but this difference decreased over time.

Conclusions: Although it may be preferable to administer propofol TCI by using a locally derived parameter set, it is acceptable to use a model from elsewhere. The Marsh and Tackley models produced equally good performance and are appropriate for propofol TCI within the range of 3-6 micro gram/ml. The Dyck model was less accurate at maintaining anesthetic concentrations, possibly because it was derived from low concentrations. Concentrations in blood, the most sensitive indicators of performance, demonstrated differences among the parameter sets. Clinically, TCI worked well, and by clinical criteria, the choice of pharmacokinetic model did not appear to make a difference.

COMPUTER-ASSISTED target controlled infusions (TCI) of intravenously administered anesthetic drugs have been investigated and successfully implemented in clinical practice. [1-9] These techniques use averaged pharmacokinetic models derived from population samples. Investigators who have assessed the accuracy of TCI report inevitable variation of achieved concentrations in blood around the targeted concentration. [1-10] Nevertheless, it has been shown that a mean variation of measured concentrations of 20-30% greater or lesser than targeted concentrations with a maximum of 50-60% can be considered clinically acceptable and that achievement of greater accuracy is unlikely. [2,11].

Possible sources of variability arise during estimation of the pharmacokinetic parameters and during use of the model for TCI. For example, variance exists among the parameters of a polyexponential function fitted to a single set of concentration-time data. [12] In addition, there is pharmacokinetic variation among the subjects who constitute the sample selected for derivation of the averaged parameter set. Often, for cost consideration, the number of subjects in the sample is small, casting doubt as to whether the sample can be assumed to represent the population adequately. Furthermore, patients receiving TCI do not necessarily belong to the same population from whom the original pharmacokinetic model was derived, and the effects of the surgical procedure can result in pharmacokinetic variability within each patient. [13].

All of these factors can lead to bias and inaccuracy of the concentrations achieved during

TCI. It is not known with certainty which parameter set is the most suitable for general use in a TCI system. The aims of this investigation were therefore to determine whether the selection of a pharmacokinetic parameter set for propofol TCI significantly influences the resulting plasma propofol concentrations and clinical acceptability of the technique.

Materials and Methods

Institutional approval having been granted, informed consent was obtained from 30 nonobese patients, American Society of Anesthesiologists physical status 1 or 2, 21-50 yr old, and weighing 40-90 kg. All patients were scheduled for orthopedic or gynecologic surgery. Patients received total intravenous anesthesia with propofol TCI supplemented by constant-rate sufentanil infusions. They were randomly assigned into one of three groups of ten each, and each group was allotted one of three pharmacokinetic models to be used for propofol TCI. The parameter sets were obtained from published reports, and the groups were designated according to these reports as "Tackley" (Tackley et al. [5]), "Marsh" (Marsh et al. [14]), and "Dyck" (Dyck and Shafer*) (Table 1 and Table 7). Propofol TCI was administered with a syringe pump (22, Harvard Apparatus, South Natick, MA) connected to a personal computer with an RS-232c interface and running the program Stanpump.**

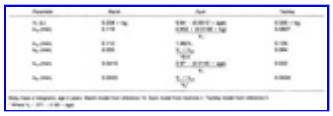
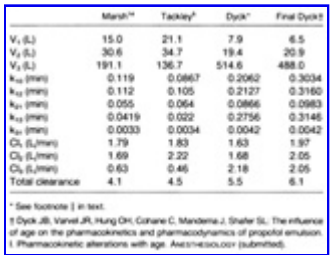


Table 1



	Marsh[14]	Tackley[5]	Dyck*	Final Dyck†
V_1 (L)	15.0	21.1	7.9	6.5
V_2 (L)	30.6	34.7	19.4	20.9
V_3 (L)	191.1	136.7	514.6	488.0
k_{10} (/min)	0.119	0.0867	0.2062	0.3034
k_{12} (/min)	0.112	0.105	0.2127	0.3160
k_{21} (/min)	0.055	0.064	0.0866	0.0983
k_{13} (/min)	0.0419	0.022	0.2756	0.3146
k_{31} (/min)	0.0033	0.0034	0.0042	0.0042
Cl_1 (L/min)	1.79	1.83	1.63	1.97
Cl_2 (L/min)	1.69	2.22	1.68	2.05
Cl_3 (L/min)	0.63	0.46	2.18	2.05
Total clearance	4.1	4.5	5.5	6.1

* See footnote] in text.

† Dyck JB, Varvel JR, Hung OH, Cohane C, Manderna J, Shafer SL. The influence of age on the pharmacokinetics and pharmacodynamics of propofol emulsion I. Pharmacokinetic alterations with age. Anesthesiology (submitted).

Table 7

Diazepam 10 mg was administered orally for pre-medication. Before induction of anesthesia the following vessels were cannulated, after administration of regional anesthesia:

- a forearm vein for administration of intravenous fluids and drugs

- an external jugular vein for obtaining venous blood samples to measure venous propofol concentrations

- a radial artery for continuous measurement of arterial blood pressures and for obtaining blood samples for measurement of arterial propofol concentrations

After attachment of electrocardiograph electrodes and preoxygenation, sufentanil was administered. Initially 0.5 micro gram/kg was administered over a 20-s period and was

followed by an infusion of 0.5 micro gram *symbol* kg sup -1 *symbol h sup -1 administered by syringe pump (Perfusor Secura, B. Braun, Melsungen, Germany). Induction of anesthesia commenced 4-5 min later with administration of propofol TCI.

Vecuronium 0.085 mg/kg was used to provide muscle relaxation, which was monitored with a train-of-four nerve stimulator. No additional incremental doses of vecuronium were given. After tracheal intubation, the patients' lungs were ventilated with an air-oxygen mixture (40% oxygen), with maintenance of the end-expired carbon dioxide concentration at 4.5-5%. The sufentanil infusion was terminated 20-30 min before the anticipated end of surgery and the propofol infusion 10-15 min before the end of surgery. Residual muscle relaxation was reversed at the end of surgery with glycopyrrolate 0.0085 mg/kg and neostigmine 0.035 mg/kg.

The targeted propofol concentrations were as follows:

- For induction of anesthesia and tracheal intubation the targeted concentration was 4 micro gram/ml.

- To test the ability of the model to follow changes to dosage rates, a stepwise decrease and an increase to the targeted concentrations were introduced 10-20 min after induction of anesthesia. The initial targeted concentration (4 micro gram/ml) was decreased to 3 micro gram/ml for 10 min and then increased again to 4 micro gram/ml for 10 min, after which surgery began.

- During surgery, and provided there was no hypotension (defined as a reduction of systolic blood pressure by more than 30% of the preinduction value), targeted concentrations were increased to 5-6 micro gram/ml for 15 min, after which targeted concentrations were again decreased to those appropriate for surgery to the individual patient. If patients exhibited signs of light anesthesia, targeted propofol concentrations were increased by 20%. Light anesthesia was judged by any of the following clinical signs: an increase in systolic blood pressure by more than 15 mmHg greater than preinduction values; an increase in heart rate by more than 15 beats/min of preinduction values; or tearing or sweating.

- During wound closure targeted propofol concentrations were 2 micro gram/ml.

Hypotension was treated by reducing targeted propofol concentrations by 25% and appropriate treatment with intravenous fluid administration or glycopyrrolate 0.007 mg/kg if the heart rate was less than 60 beats/min.

Arterial and venous blood samples (4 ml) for measurement of serum drug concentrations were obtained at the following times:

- 10-20 min after induction of anesthesia (before decreasing the targeted concentration from 4 to 3 micro gram/ml)

- in association with the stepped decrease and increase in targeted concentrations (described

above) at 2, 5, and 10 min after each adjustment to the targeted concentration

- every 15-20 min subsequently or before adjusting the targeted propofol concentration

Heart rate and arterial blood pressures were recorded at the following times: before induction of anesthesia, immediately before and after intubation, before skin incision, and 5 min after skin incision.

Measurement of Propofol Concentrations in Serum

Blood samples were allowed to clot and were centrifuged at 3,000 rpm for 10 min, and the serum was frozen at -4 degrees Celsius. The following were added to 500 micro liter serum placed in a polypropylene test tube: internal standard consisting of 5 micro liter thymol (250 micro gram/ml in ethyl alcohol), 500 micro liter KH_2PO_4 (0.1 M), 1 ml ethyl acetate, and 50 micro liter tetramethyl ammonium hydroxide (0.2 M). Extraction was conducted on a slow rocking apparatus for 15 min. The mixture was centrifuged at 3,000 rpm for 10 min, and a 200-micro liter aliquot of the upper ethyl acetate phase was removed by pipette for direct injection into a high-pressure liquid chromatograph (IsoChromLC pump, Spectra Physics, San Jose, CA). Analysis was performed on a 250 X 4.6-mm column (Partisil 5C8, Phenomenex, Torrance, CA). The eluent consisted of acetonitrile:water 85% and orthophosphoric acid (40:20:0.1 ml). Propofol and thymol were detected by fluorescence at 310 nm after excitation at 276 nm (Spectra System FL2000, Spectra Physics). The areas under the chromatographic peaks were displayed graphically and calculated with an integrator (Data Jet CH1, Spectra Physics). For each batch of blood samples (from one patient) a separate standard curve was computed by adding pure propofol liquid to drug-free human serum to make up concentrations of 0.7, 1.5, 3, 4, 6, 8, and 12 micro gram/ml. Linear regression (method of least squares) was used with serum propofol concentration as the dependent variable and the ratio of the areas under propofol and internal standard chromatographic peaks as the independent variable. Propofol concentrations in test serum were calculated by using the obtained regression equation. The lower limit of detection was 15 ng/ml, and the coefficient of variation was 8.4%.

To determine whether propofol concentrations measured in human blood, plasma, and serum differ significantly, 65 venous blood samples (10 ml) were obtained from ten healthy patients receiving propofol infusions for anesthesia. Five milliliters of each sample was placed in a tube containing anticoagulant (ethylenediamine tetraacetic acid), and 5 ml was allowed to clot in a tube prepared with silicon. The samples were immediately placed in a refrigerator (4 degrees Celsius). Clotted blood samples were centrifuged at 3,000 rpm, and the serum was frozen at -4 degrees Celsius. Half of each anticoagulated blood sample was centrifuged, and the plasma was frozen. The remaining whole blood was stored at 4 degrees Celsius. Propofol concentrations were measured within 48 h of sampling by using separate standard curves compiled for human serum, plasma, and blood.

Data Analysis

Calculations.

For each blood sample the percentage prediction error (PE) of the predicted concentration in plasma was calculated according to the formula [10] Equation 1 PE is an indication of the bias of the achieved concentrations, and the absolute value PE ([vertical bar] PE [vertical bar]) is a measure of the precision (inaccuracy). In addition, the difference between the measured arterial and venous concentrations (AV difference) was calculated and tabulated.

$$PE = \frac{measured - predicted}{predicted} \times 100$$

Equation 1

Data were analyzed using computer software (Statgraphics, version 5.0, Statistical Graphics, Rockville, MD). Tests for normality of distribution were performed by examination of box-and-whisker plots and by distribution-fitting procedures (Kolmogorov-Smirnov test). Descriptive statistics included means, SD, medians, 10th and 90th percentiles and the 95% confidence intervals (CI) for the means (or medians if the data did not fit a normal distribution). A significant difference between groups was accepted if the 95% CI for the difference between means or medians did not include zero) (alpha < 0.05).

For comparison of cardiovascular and demographic data, intergroup comparisons were made using one-way analysis of variance (ANOVA). Ordinal data were analyzed by the chi-squared (Fisher's exact) test. Propofol concentrations in whole blood, plasma, and serum were compared using Friedman's nonparametric two-way ANOVA followed by Wilcoxon's paired signed-ranks test. A difference between medians was accepted as significant if $P < 0.01$.

Analysis of Groupwise Pooled Data

Drug concentration and PE data were pooled in each group, and intergroup comparisons were made by multifactor ANOVA with the following variables as covariates: at sampling, the time elapsed since induction of anesthesia; the predicted drug concentration; and the time elapsed since changing of the targeted concentration. In addition, regression analysis with stepwise variable selection was used to determine the extent to which variation of the aforementioned variable explained variation in the concentration data. Post hoc range tests were performed using Scheffe's method: a difference between means was accepted as significant if the 95% CI did not include zero. If data did not fit a normal distribution, distribution-free nonparametric methods were used with Kruskal-Wallis ANOVA and calculation of the 95% CI of the medians and their differences [15] with the Confidence Interval Analysis computer program.**

Intrasubject Data Analysis

The PE data from each subject were evaluated according to the recommendations of Varvel

et al. [10] For each patient, four indicators of predictive performance were calculated:

Median Absolute Prediction Error.

The percentage median absolute prediction error (MDAPE) indicates the inaccuracy of TCE in the ith subject Equation 2 where N sub i is the number of [vertical bar] PE [vertical bar] values obtained for the ith subject.

$$MDAPE_i = \text{median}\{|PE|_{ij}, j = 1, \ldots, N_i\}$$

Equation 2

Median Prediction Error.

The percentage median prediction error (MDPE) reflects the bias of TCI in the ith subject: Equation 3.

$$MDPE_i = \text{median}\{PE_{ij}, j = 1, \ldots, N_i\}$$

Equation 3

Divergence.

The divergence is a measure of how resulting drug concentrations in a subject are affected by time. It is defined as the slope of the linear regression equation of [vertical bar] PE [vertical bar] against time and is expressed in units of percentage divergence per hour. A positive value indicates progressive widening of the gap between predicted and measured concentrations, whereas a negative value reveals that the measured concentrations converge on the predicted values.

Wobble.

Wobble is another index of the time-related changes in performance and measures the intrasubject variability in performance errors. In the ith subject the percentage wobble is calculated as follows: Equation 4.

$$wobble_i = \text{median}\{|PE_{ij} - MDPE_i|, j = 1, \ldots, N_i\}$$

Equation 4

Subsequent Data Analysis

Box-and-whisker plots of MDAPE, MDPE, divergence, and wobble were compiled to compare patients within each of the three groups, and Kruskal-Wallis one-way ANOVA was used to detect a difference between groups. To examine visually the performances of each pharmacokinetic parameter set over time, the following graphs were created for each group:

- The results from the individual patients exhibiting the best, median, and worst performances (as judged by the MDAPE) were plotted, with the predicted concentrations represented by a continuous line and the measured concentrations by discrete dots.

- Graphs of measured values divided by the predicted values were plotted on a semi-logarithmic scale over time. These graphs provided a means to visually assess the extent of bias, precision, wobble and divergence in each group.

- Wobble was demonstrated by plots of (PE_{ij} - $MDPE_1$) over time (where j = 1 .... N_i in the ith subject).

- Divergence was illustrated by plots of the regression lines for (PE_{ij} - $MDPE_i$) on time. These graphs provided a means to visually assess how the errors in each patient tended to differ over time from that patient's own MDPE.

Results

Thirteen men and 17 women were included in the study. Demographic information is summarized in Table 2. The predicted values were not normally distributed. The median predicted values for the Dyck, Marsh, and Tackley groups were 3.0, 4.0, and 3.0 respectively (95% CI = 3-4 for all three groups). Nonparametric ANOVA (Kruskal-Wallis) and calculation of the 95% CI between the medians indicated that there were no differences between the predicted propofol concentrations for the three groups. The total numbers of measured arterial concentrations for the three groups were Marsh = 101, Dyck = 107, and Tackley = 116. The total numbers of venous concentrations measured were Marsh = 98, Dyck = 101, and Tackley = 112.

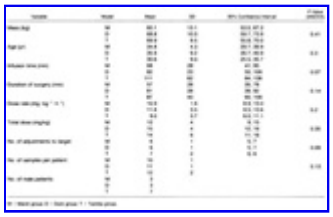


Table 2

Arterial Concentrations

Groupwise Pooled Data.

Information obtained from the groupwise pooled data is summarized in Table 3 and in Figure 1 and Figure 2. The mean measured arterial propofol concentrations were significantly greater in the Dyck group than in the Marsh and Tackley groups (P < 0.00001).

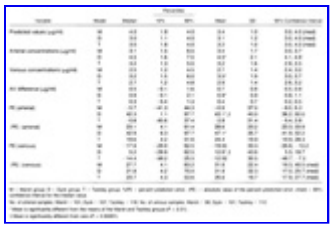


Table 3

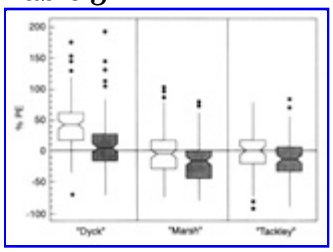


Figure 1

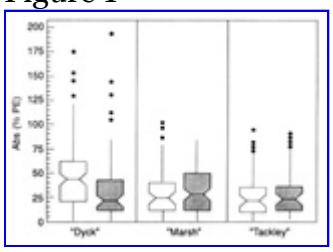


Figure 2

The arterial mean prediction error (MPE) for the Dyck group was 43.1% (95% CI = 36.2-50.0%) and this differed significantly from zero and from the Marsh and Tackley groups ($P < 0.00001$). The arterial MPE for the Marsh and Tackley groups were -0.9% (95% CI -8.0-+6.3%) and -2.8% (95% CI -9.4-+3.8%) respectively: the values for these two groups did not differ from zero or from each other.

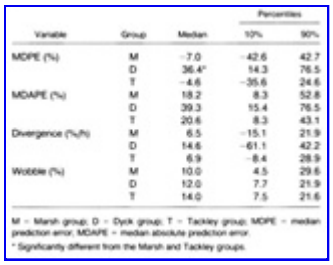
The arterial mean absolute prediction error (M [vertical bar] PE [vertical bar]) for the Dyck group was 47.1% (95% CI = 41.9-52.2%), which differed significantly from the Marsh and Tackley groups ($P < 0.00001$) whose mean values were 28.6% (95% CI = 23.3-33.9%) and 24.4% (95% CI = 19.4-28.3%), respectively. The values for the Marsh and Tackley groups did not differ from each other.

Regression analysis by stepwise variable selection revealed that in all three groups the PE and [vertical bar] PE [vertical bar] were minimally influenced by the time of sampling (from the time of induction of anesthesia), the targeted concentration, and the time that had elapsed since the previous adjustment to the targeted concentration (R^2 = 4-5%).

During the formalized stepped changes in targeted concentrations that took place before commencement of surgery, ANOVA of the various PE revealed that within each group, there were no significant differences between the samples drawn at various time intervals (2, 5, and 10 min after adjustments to the targeted concentrations).

Intrasubject Performance.

The median values for each group for MDPE, arterial MDAPE, divergence, and wobble are depicted in Table 4. MDPE was significantly higher in the Dyck group, whereas there were no significant differences between groups for MDAPE, divergence, and wobble.



Variable	Group	Median	Percentiles 10%	Percentiles 90%
MDPE (%)	M	−7.0	−42.6	42.7
	D	36.4*	14.3	76.5
	T	−4.6	−35.6	24.6
MDAPE (%)	M	18.2	8.3	52.8
	D	39.3	15.4	76.5
	T	20.6	8.3	43.1
Divergence (%/h)	M	6.5	−15.1	21.9
	D	14.6	−61.1	42.2
	T	6.9	−8.4	28.9
Wobble (%)	M	10.0	4.5	29.6
	D	12.0	7.7	21.9
	T	14.0	7.5	21.6

M = Marsh group, D = Dyck group, T = Tackley group, MDPE = median prediction error, MDAPE = median absolute prediction error.
* Significantly different from the Marsh and Tackley groups.

Table 4

(Figure 3) depicts the patients with the best, median and worst performance from each group. The Dyck parameter set consistently underpredicted the concentrations so that the measured concentrations were generally much higher than those estimated by the program. The Marsh and Tackley parameter sets overpredicted the concentrations during the 1st 20 min so that the measured concentrations were lower than predicted during that time. These impressions are confirmed by Figure 4, which plots the ratio of the measured value to the predicted value for each patient and shows that in the Dyck group, the ratio is in general greater than unity (i.e., MDPE is positively biased). In the other two groups (Marsh and Tackley) the ratio was less than unity during the 1st 20 min. The Tackley group appeared to have the least degree of scatter in Figure 4 (inaccuracy).

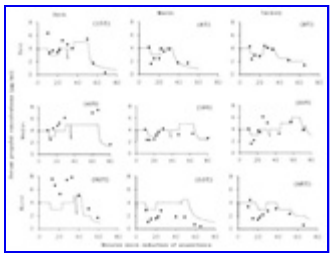


Figure 3

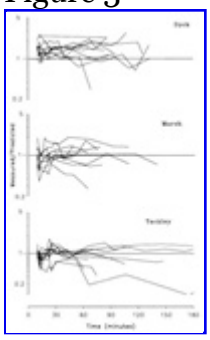


Figure 4

(Figure 5) depicts wobble by plotting in each patient the difference between each PE and the MDPE for that patient (PE_{ij} - $MDPE_i$). This plot shows that there was a greater degree of variation about each patient's MDPE in the Dyck group even though no statistically

significant difference in wobble was found between the groups. Figure 6, which depicts the regression lines for PE - MDPE over time, illustrates that in the three groups the tendencies for the errors to wander from each patient's own MDPE were similar.

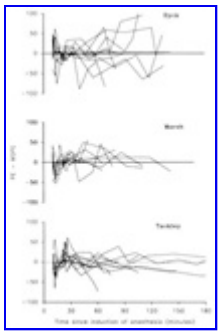


Figure 5

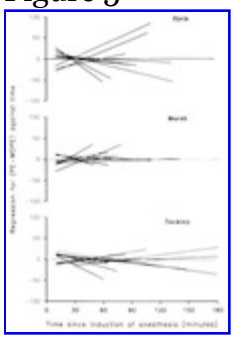


Figure 6

Venous Concentrations

The venous concentrations were significantly greater in the Dyck group (P = 0.002). In all three groups the venous concentrations were significantly less than arterial concentrations (P < 0.05). The overall AV difference was 0.6 micro gram/ml (95% CI = 0.5-0.7 micro gram/ml). Linear regression analysis by stepwise variable selection demonstrated a positive association between the AV differences and the measured arterial concentrations (R^2 = 30%; P < 0.00001), and a negative association with with the time of sampling (R^2 = 11%; P < 0.00001). There was no association between the AV differences and the venous concentrations. Figure 7(A) illustrates how the AV differences increased with the arterial concentrations. Figure 7(B) shows that the greatest AV differences were to be found during the 1st 20 min of the infusion. The propofol AV differences for the Dyck, Marsh, and Tackley models were 0.9 micro gram/ml (95% CI = 0.8-1.1), 0.7 micro gram/ml (95% CI = 0.5-0.8), and 0.4 micro gram/ml (95% CI = 0.2-0.5), respectively. The Dyck group AV differences were significantly higher than the Marsh and Tackley groups (P < 0.00001).

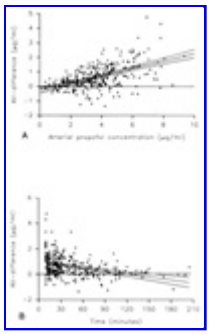


Figure 7

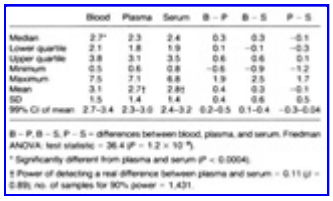
The venous MPE are depicted in Figure 1 and Table 3 and for the Dyck group was 12.6% (95% CI = 5.5-19.7%). These values were significantly different (P < 0.00001) from those of the Marsh and Tackley groups, whose values were -19.9% (95% CI -26.6--13.2%) and -12.9% (95% CI-48.7--7.2%). The values for the Marsh and Tackley groups did not differ from each other. In all three groups the venous MPE differed significantly from zero (P < 0.00001).

The venous [vertical bar] PE [vertical bar] are depicted in Figure 2 and Table 3. The data were not normally distributed and therefore it is more appropriate to examine the median values in Table 3. The median values for the Dyck, Marsh, and Tackley groups were 21.8% (95% CI = 17.0-25.7%), 27.7% (95% CI = 18.3-40.5%), and 23.7% (95% CI = 17.9-27.7%). Nonparametric ANOVA (Kruskal-Wallis) and calculation of the 95% CI for the differences between the medians indicated that the venous [vertical bar] PE [vertical bar] did not differ significantly among the three groups.

The venous MPE was significantly less than than the arterial MPE in all three groups (Figure 1). The venous [vertical bar] PE [vertical bar] of the Dyck group was significantly less than the arterial [vertical bar] PE [vertical bar] in the same group (P = 0.0003, Mann-Whitney U test), whereas in the other two groups the venous and arterial values for [vertical bar] PE [vertical bar] did not differ (Figure 2).

Comparison of Concentrations in Whole Blood, Plasma, and Serum

Comparisons of measured concentrations among whole blood, plasma, and serum are presented in Table 5. Significant differences were found between blood and plasma (P = 1.2 x 10 sup -8) and between blood and serum (P = 5.1 x 10 sup -4). There was no significant difference between the concentrations in plasma and serum. The power of detecting a real difference between plasma and serum at an alpha level of 0.05 was calculated to be 0.11.



	Blood	Plasma	Serum	B - P	B - S	P - S
Median	2.7*	2.3	2.4	0.3	0.3	-0.1
Lower quartile	2.1	1.8	1.9	0.1	-0.1	-0.3
Upper quartile	3.8	3.1	3.5	0.6	0.6	0.1
Minimum	0.5	0.6	0.8	-0.6	-0.9	-1.2
Maximum	7.5	7.1	6.8	1.9	2.5	1.7
Mean	3.1	2.71	2.81	0.4	0.3	-0.1
SD	1.5	1.4	1.4	0.4	0.6	0.5
95% CI of mean	2.7-3.4	2.3-3.0	2.4-3.2	0.2-0.5	0.1-0.4	-0.3-0.04

B - P, B - S, P - S = differences between blood, plasma, and serum. Friedman ANOVA: test statistic = 36.4 (P = 1.2 x 10 *).

* Significantly different from plasma and serum (P < 0.0004).

† Power of detecting a real difference between plasma and serum = 0.11 (d = 0.89); no. of samples for 90% power = 1,431.

Table 5

Cardiovascular Effects

There were no significant intergroup differences in mean arterial pressures and heart rate at the recorded times (before induction of anesthesia, immediately before and after intubation, before skin incision, and 5 min after skin incision). Hence data from the three groups at these stages were pooled and subjected to one-way ANOVA followed by multiple range analysis using Tukey's HSD procedure for post hoc comparisons with 99% CI for the mean. Hemodynamic data are summarized in Table 6. Mean arterial pressure decreased significantly from mean awake values of 104 mmHg (SD = 13; 99% CI = 98-112) to 77 mmHg (SD = 13; 99% CI = 68-85) before intubation and remained significantly less than preinduction values until 5 min after skin incision when mean arterial pressure increased significantly to values that were similar to the awake values (97 mmHg; SD = 19; 99% CI = 88-105). Heart rates before and after intubation were greater than, but not significantly different from awake values, and slowed significantly before skin incision and 5 min thereafter to values similar to the awake values. Altogether 7 patients required downward adjustments to their targeted concentrations because of hypotension (2 in the the Dyck group, 1 in the Marsh group, and 4 in the Tackley group). During surgery, 12 patients developed hypertension necessitating increases in their targeted concentrations. Of these, 4, 3, and 5 were in the Dyck, Marsh, and Tackley groups, respectively. There were no significant intergroup differences in the numbers of patients who required adjustments to their targeted propofol concentrations because of hypotension or signs of light anesthesia.

Table 6

Discussion

Selection of Pharmacokinetic Parameter Sets for Targeted Controlled Infusion

The principle aim of the investigation was to determine whether the choice of a pharmacokinetic parameter set for propofol TCI significantly influences the resulting drug concentrations, given the possible pharmacokinetic disparity among patient populations and the influences of surgery on pharmacokinetics. In this study three pharmacokinetic models that had been derived from patient samples from two continents were used in studying a group of patients on a third continent. Two of the parameter sets (Marsh and Tackley) were selected because they had been derived from studies in which infusions maintained anesthetic concentrations for 1-2 h, and they were therefore considered likely to produce good agreement between measured and predicted concentrations. The Dyck parameter set originated from a study of infusions of short duration but was considered useful because it adjusts for patient mass and age. We used the authors' initially derived parameter set that had been published in a proceedings.* They have subsequently addressed the influences of three modeling techniques on their data,**** and their final parameter set is only slightly different from the set that we used in our study (Table 7).

Performance of the Three Parameter Sets

During anesthesia similar alterations in targeted concentrations were deliberately made to all patients to test the ability of the models to achieve a variety of drug concentrations. The Dyck group experienced significantly greater arterial and venous concentrations and a positive bias (arterial MPE 43%). In other words, in the Dyck group the concentrations were considerably greater than predicted (i.e., targeted) values. The Marsh and Tackley groups performed well (arterial MPE -0.9% and -2.8%, respectively). The Dyck group also had the worst precision (arterial M [vertical bar] PE [vertical bar] 47%), whereas in the other two groups precision was significantly better (24-28%). These conclusions are supported by analysis of the intrasubject PE, the MDPE. There was no significant difference in MDAPE; however, the numbers were small (n = 10) and variances large, and it would therefore require inclusion of a greater number of patients to detect a difference in MDAPE with confidence.

During the formalized changes to the targeted concentrations that were introduced before the commencement of surgery (stepped down from 4 to 3 micro gram/ml for 10 min and then stepped up from 3 to 4 micro gram/ml), there were no significant differences in the various PE obtained at 2, 5, and 10 min after the changes. This indicates that all three models enabled the computer to faithfully follow acute changes in parallel with targeted concentrations and that the direction of change did not influence the results. In addition, during the later course of the anesthetic, the errors were not increased by the subsequent passage of time, as indicated by the minimal influence on the various PE by the time elapsed since induction of anesthesia and the time elapsed since the previous adjustment to the targeted concentrations. These conclusions are supported by the low values for within-patient divergence and wobble in each group.

Selection of Targeted Concentrations

The targeted concentrations for propofol were based on the recommendations of authors [16,17] who reviewed studies in which propofol infusions had been supplemented by nitrous oxide and by opioid infusions and the recommendations of authors who studied the pharmacodynamics of propofol given alone. [18] For sufentanil, the use of bolus and constant infusion rate should, in most patients, lead to analgesic concentrations of approximately 0.5 ng/ml, [16,19] and it appears that in all three groups the patients were sufficiently anesthetized to prevent reaction to intubation or skin incision. During subsequent surgery, similar numbers of patients in all three groups developed increased arterial pressures that were sufficient to warrant increasing the targeted propofol concentrations. There were no other clinical signs of inadequate anesthesia, and furthermore, after patients had sufficiently recovered from the initial neuromuscular block (as indicated by train-of-four monitoring), no patient in any of the three groups moved in response to surgery.

Hemodynamic Changes

Reductions in arterial blood pressures occurred after induction of anesthesia and to a similar extent in all three groups. Furthermore, similar numbers of patients in the three groups had sufficient hypotension to require reductions in their targeted propofol concentrations. However, heart rate and arterial blood pressure measurements do not provide adequate assessment of cardiovascular function, for which it is necessary to take into consideration other variables, such as cardiac output. In this study, therefore, it cannot be concluded that one group did not have greater cardiovascular depression than the others.

Evidence Suggestive of Nonlinear Propofol Pharmacokinetics

The Dyck parameter set was less accurate in maintaining targeted concentrations of 3-6 micro gram/ml: however it is remarkable that, considering the disparity of the population samples, application of the Marsh and Tackley sets resulted in low bias and acceptable degrees of accuracy. The reasons for the underprediction by the Dyck set should therefore not be sought in the dissimilarity of the populations but rather in the method used for deriving the parameter sets. The Dyck set was obtained by administering rapid infusions lasting 6-11 min (0.5 mg sup -1 *symbol* kg sup -1 *symbol* min sup -1 until the occurrence of electroencephalographic isoelectricity or hypotension). Blood samples were collected for as long as 19 h. Therefore, although the initial concentrations were high (average peak value 8.6 micro gram/ml), they decreased rapidly after the infusion so that the majority of blood samples thereafter contained subanesthetic concentrations of propofol. Using their finally derived parameter set, the authors of the Dyck study retrospectively compared the measured concentrations and those predicted by computer simulations.**** They noted that the measured peak concentrations were consistently greater than predicted and that after 400 min the relation was reversed; that is, the measured concentrations were less than predicted. They suggest that these phenomena can be explained by nonlinear propofol pharmacokinetics: whereby at high concentrations, liver blood flow is reduced, leading to reduced clearance: Concurrently, a reduced cardiac output at the greater concentration would result in slower distribution to peripheral compartments. The Dyck parameter set has been tested at low concentrations by administering propofol TCI for sedation to patients requiring mechanical ventilation in an intensive care unit.***** The measured concentrations were approximately 50% less than predicted and this provides additional evidence that propofol pharmacokinetics may be nonlinear.

The results of our study support the hypothesis further. It can be surmised that because propofol disposition is more rapid at low concentrations, the Dyck parameter set (which is based principally on subanesthetic concentrations), underpredicted the concentrations resulting from an infusion regimen designed to maintain anesthesia. In other words, the Dyck set expected faster kinetics and therefore called for more rapid infusion rates, that resulted in greater concentrations. The results from our study are valid only for the range of concentrations studied and cannot be extended to include higher or lower concentrations. Nevertheless one may conjecture that should the Marsh and Tackley sets be used to provide sedation by TCI, the resulting propofol concentrations would be less than predicted, because these two sets were derived from infusions that provided greater concentrations and

therefore expect slower kinetics.

The hepatic extraction ratio of propofol is high, and therefore hepatic clearance is dependent on liver blood flow. There is experimental evidence that indicates that a reduction in liver blood flow may be one of the mechanisms by which propofol changes its own pharmacokinetics. Lange et al. [20] measured hepatic plasma flow in patients scheduled for coronary artery bypass surgery. After a 2-mg/kg propofol bolus dose, flow was reduced by 14% and recovered to preanesthetic values at sternotomy. A study in dogs [21] in which propofol was infused at infusion rates increased stepwise from 200 to 500 micro gram *symbol* kg sup -1 *symbol* min sup -1 revealed a reduction in indocyanine green clearance that paralleled a dose-dependent reduction in cardiac output. Furthermore, at the fastest infusion rates, the blood propofol concentrations were greater than expected. The rapid infusion rates to these animals resulted in high concentrations (530 micro gram/ml), and the findings cannot be extrapolated to the lower concentration ranges generally used during anesthesia and sedation in humans. Using more clinically relevant concentrations (6.8 [SD = 2.6] micro gram/ml), Runciman et al. [22] and coworkers administered propofol to chronically catheterized sheep and found that hepatic and renal blood flows decreased. Propofol has been shown to decrease cardiac output in animals dose-dependently [23,24] and in humans. [25-27] A reduced cardiac output will additionally influence the pharmacokinetics of propofol by reducing the rate of distribution to peripheral tissues and possibly by contributing to a reduction of hepatic blood flow.

Are Propofol Nonlinear Kinetics Clinically Relevant?

Is the accumulated evidence indicating nonlinear propofol pharmacokinetics clinically important? The data from this and other investigations are too few and the concentration range too narrow to derive a model that adjusts for different concentration ranges. It is unknown whether depression of myocardial contractility and cardiac output exhibits in humans a similar time-related hysteresis as found in pigs by Coetzee et al. [23] In that study decreased myocardial contractility and cardiac output did not return to preinfusion values despite a rapid reduction in propofol concentrations. The question arises whether on lowering the concentrations, the effects of propofol on the circulation will be rapidly reversed, returning the pharmacokinetics to those normally found at low concentrations. A prospective study that addresses the issue of different pharmacokinetics at various concentrations is needed to further substantiate the hypothesis that the pharmacokinetics of propofol are consistently nonlinear and to derive a model that compensates for the influence of propofol on its own pharmacokinetics.

Concentrations in Whole Blood, Plasma, and Serum

Whole-blood propofol concentrations were used in the three studies in which the pharmacokinetic parameter sets were derived. [5,14]* We measured concentrations in serum

and in a separate investigation found that concentrations in whole blood were significantly greater than concentrations in plasma and serum in the range 0.5-7.5 micro gram/ml. The differences were small (Table 5), and it is unlikely that they were large enough to have influenced our conclusions with regard to the concentrations achieved and the prediction errors. There was no significant difference between concentrations in plasma and serum, and the sample size required to increase the power of detecting a real difference to 90% would need to be increased to approximately 1,400 samples.

Arterial Versus Venous Measurements

The AV differences in concentrations illustrate that using venous concentrations to evaluate the bias and precision of TCI can lead to different conclusions. Whereas the arterial values indicate negligible bias for the Marsh and Tackley groups, the negative venous PE suggest that these two models tend to overpredict concentrations in blood, leading to underdosing. The venous positive bias achieved by the Dyck group is considerably less than that group's arterial values (by approximately 25%). Furthermore, venous [vertical bar] PE [vertical bar] s erroneously suggest that the degree of inaccuracy was similar in all three groups. The positive association detected between arterial propofol concentrations and the AV differences can partially explain the finding that AV differences were greater in the Dyck group who also experienced significantly greater arterial concentrations.

The Dyck parameter set was derived from arterial blood samples and the Marsh set from a modification of a model published by White and Kenny [28] and Gepts et al., [29] in which arterial sampling was performed. The Tackley set was calculated after venous sampling. When comparing predicted and measured concentrations, the sampling site used for modeling and for evaluation and the time of sampling may influence the results. Chiou [30,31] has reviewed the phenomenon of dependence of drug concentration on sampling site and has pointed out that profiles of concentration in blood or plasma from different sampling sites can lead to the calculation of widely differing pharmacokinetic parameters. The significant arteriovenous propofol concentrations occurring during our TCI study differ from the findings of Major et al., [32] who, using the previous propofol formulation in Cremophor-EL found negligible AV differences in concentration after a single propofol dose (2 mg/kg administered over a 60-s period) provided 1 min had elapsed after administration of the dose. Theoretically, after an intravenous bolus dose the AV differences are greatest initially (with the arterial concentrations greater) and then the relation may be reversed. 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 rapidly distributed into the tissues. This difference will diminish as the tissues become saturated until after some minutes the arterial and venous concentrations are the same. If the infusion is now stopped, the arterial concentrations will decrease rapidly as drug is removed from portal and hepatic arterial blood by the liver. Peripheral tissues however do not metabolize drug, so that drug will now be added to venous blood slowing the rate of decrease in venous concentrations or even reversing the relation between arterial and venous

concentrations. After some time when the arterial concentrations are decreasing less rapidly, and some drug has been "washed out" from the tissues, the arterial and venous concentrations will again be similar.

In our study, the AV difference of the first samples (which were drawn at approximately 10 min after starting the infusion) was 1.3 micro gram/ml (95% CI = 0.3-2.4 micro gram/ml). Therefore equilibrium between arterial and venous blood had not occurred by this time. Table 8 summarizes the AV differences that occurred in 22 patients in whom arterial and venous concentrations could be followed during the stepped-down and stepped-up procedure that ensued. Two minutes after decreasing the targeted concentrations from 4 to 3 micro gram/ml the AV differences had decreased significantly, from 1.7 to 0.5 micro gram/ml. Had the venous concentrations not lagged behind the arterial concentrations during this time, the AV difference would have been maintained.

Minutes Since Start	Minutes Since Changing Target	Predicted Concentration* (μg/ml)	AV Difference (μg/ml)
10	10	4	1.7† (1.4–2.1)
12	2	3	0.5 (0.2–0.9)
15	5	3	0.6 (0.3–1.0)
20	10	3	0.7 (0.4–1.0)
22	2	4	0.8 (0.4–1.1)
25	5	4	0.9 (0.6–1.3)
43 (37–48)	20 (16–24)	4.1 (4.0–4.2)	0.6 (0.2–0.9)

Data from 22 patients in whom AV differences could be followed. Values in parentheses are the 95% confidence intervals for the means.

* Concentration predicted by the program Stanpump.

† Significantly different from subsequent AV differences [analysis of variance for repeated measures ($P < 0.0001$) and Tukey HSD post hoc test for paired differences].

Table 8

After 10 min at the new targeted concentration of 3 micro gram/ml, the targeted concentrations were again increased to 4 micro gram/ml, and the AV differences increased slightly 2 and 5 min later, but not significantly. At 43 min after starting the infusion the AV differences were small (0.6 micro gram/ml). In our study a negative association was found between the AV differences and the time of sampling (R^2 = 11%) and it is possible that this association would have been stronger, had the study design been based on maintaining a constant propofol concentration throughout, instead of deliberately varying the targeted concentrations.

Why then did the Tackley parameters, which had been derived from venous sampling, perform so well? It is possible that the greater measurements in whole blood obtained in the Tackley study offset their smaller venous concentrations, as compared with our study, in which the measured concentrations in serum were less and the arterial concentrations greater. A more likely explanation is that the majority of blood samples in the Tackley study were obtained at times when venous concentrations were close to arterial concentrations and therefore it is not surprising that their derived parameters provided good predictions of the arterial concentrations in our patients. Furthermore, our targeted concentrations were generally close to those of the Tackley study and it should be emphasized that our results cannot be extrapolated beyond the concentration range and the time-frame in which the data were obtained, especially in the light of the gathering evidence that the pharmacokinetics of

propofol are nonlinear.

We recommend that arterial concentrations are more meaningful indicators for TCI than venous concentrations, as it is the arterial blood that delivers drug to the targeted organs and it is arterial concentrations that will eventually equilibrate with the effect sites. Venous concentrations merely reflect averaged concentrations from the organs from which blood is being drained, which do not usually include the effect-sites. An hypothesis that internal jugular venous concentrations are better indicators of cerebral effect-site drug concentrations remains to be tested by pharmacokinetic-pharmacodynamic studies. It is therefore preferable to evaluate propofol TCI using arterial concentrations, but venous concentrations can be used, bearing in mind that propofol venous concentrations are generally lower than arterial values by approximately 0.5-1 micro gram/ml and that sampling should be performed several minutes after an adjustment to the targeted concentration.

Differences in Dose Rates for Targeted Controlled Infusion Using the Three Parameter Sets

(Table 7) shows the pharmacokinetic parameters calculated for a 34-yr-old person weighing 70 kg. The Dyck parameters predict a smaller central (first-compartment) volume of distribution but rapid clearance (third-compartment clearance 2.18 l/min) into a volume of distribution that is very much larger than those of the other two models (third-compartment volume 515 l). Therefore, although the Dyck model requires a smaller bolus dose to fill the central compartment, a much more rapid infusion rate is needed to maintain the targeted concentration. This is illustrated by Figure 8, which depicts the infusion rates required to maintain a targeted concentration of 4 micro gram/ml for 1 h. Figure 9, which depicts the expected central compartment concentrations after stopping the simulated 1-h infusion, shows that the Dyck model predicts a more rapid decrease in the concentration in plasma because of a fast elimination clearance and rapid distribution to the third compartment.

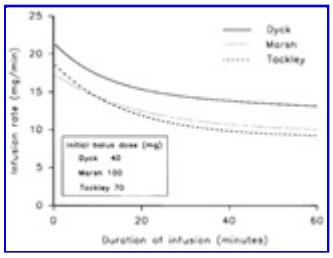


Figure 8

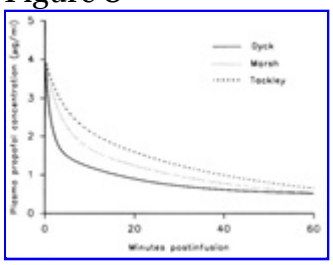


Figure 9

The patients in our study were all young to middle-aged adults (ages 21-50 [mean 33.7] yr), and one may speculate that because the Dyck parameter set is adjusted for weight and age, it would have resulted in a reduced bias and improved accuracy, had the study included elders. The infusion rates that would have been administered to a 75-yr-old person weighing 65 kg were simulated rising that facility in the program Stanpump. Figure 10 illustrates that even when taking advanced age into account, the Dyck model, when used for propofol TCI, persists in administering faster infusion rates. Furthermore the model predicts a more rapid decrease in concentrations after stopping the pump and therefore restarts the pump at an earlier stage after a lower concentration has been requested. Use of the Dyck model in ciders will therefore result in greater propofol concentrations than when using the other two models. The Marsh and Tackley models do not adjust for age, and given the known effects of age on propofol pharmacokinetics,* it is likely that if used in elders, TCI by these models will also lead to greater than expected concentrations. Furthermore, the increased concentrations in plasma could lead to adverse cardiovascular effects, given the increased susceptibility to the hemodynamic effects of propofol in elders. [33,34].

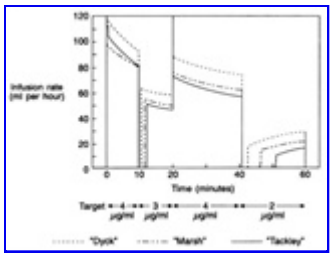


Figure 10

These considerations should not detract from the use of TCI however, as the device should be used clinically in similar fashion to a vaporizer: the anesthesiologist decides on an appropriate initial target concentration and then titrates that concentration to clinical effects. [11] That there is usually a difference between predicted and actual concentrations is not of great consequence, provided the actual concentrations are within the desired therapeutic window within which the clinician may make final adjustments to the targeted concentrations. The usefulness of TCI lies in the ability to dose more accurately, to maintain stable drug concentrations (and therefore stable effects) and to make proportional changes to the concentrations.

We conclude that although it may be preferable to administer propofol TCI by using a pharmacokinetic parameter set that has been derived from the population in question, it is acceptable to use a set that has been derived elsewhere. The pharmacokinetic parameter sets provided by Marsh et al. [14] and Tackley et al. [5] proved adequate with acceptable prediction errors, divergence, and wobble. We agree with previous investigators [35] that an important determinant of the suitability of a parameter set for TCI is that it should have been derived using a method in which TCI was performed.

Clinically, propofol TCI worked well, and the selection of a pharmacokinetic parameter set

did not appear to make a difference. The most sensitive indexes of the success of TCI were the resulting concentrations, and we found two pharmacokinetic parameter sets that accurately predicted the concentrations in blood within the range of clinical interest during anesthesia. We therefore believe that sufficient knowledge has accumulated to justify acceptance of TCI as a clinical entity and that use of these techniques should be given consideration equal to that given anesthetic vaporizers.

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**Stanpump is available for experimental use from its author. Address requests to Steven L. Shafer. M.D.: Anesthesiology Service 112A, Palo Alto Department of Veterans Affairs Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

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