British Journal of Anaesthesia **102 (5):** 626–32 (2009)
doi:10.1093/bja/aep043 Advance Access publication March 18, 2009

BJA

Evaluation of the predictive performance of four pharmacokinetic models for propofol

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Background. This study has compared the predictive performance of four pharmacokinetic models, two of which are currently incorporated in commercial target-controlled infusion pumps for the administration of propofol.

Methods. Arterial propofol concentrations and patient characteristic data were available from nine patients who, in a published study, had received a standardized infusion of propofol. Predicted concentrations with 'Diprifusor' (Marsh), 'Schnider', 'Schuttler', and 'White' models were obtained by computer simulation. The predictive performance of each model was assessed overall and over the following phases: rapid infusion (1–5 min), early (1–21 min), maintenance (21-min end-infusion), and recovery (2–20 min post-infusion).

Results. The overall assessment, based on 29–36 samples from each patient, indicated that all four models were clinically acceptable. However, the negligible bias (−0.1%) with the 'Schnider' model was accompanied by overprediction in the rapid infusion phase and underprediction during recovery. This changing bias over time was not detected as 'divergence' when assessed on absolute performance error (APE), (1.4% h^{-1}) but became significant (13.2% h^{-1}) when based on changes in signed PE over time. The 'Schuttler' model performed well at most phases but overpredicted concentrations during recovery. The White model led to a marginal improvement over 'Diprifusor' and would be expected to reduce the positive bias usually seen with 'Diprifusor' systems.

Conclusions. In assessing the predictive performance of pharmacokinetic models, additional information can be obtained by analysis of bias at different phases of an infusion. The evaluation of divergence should involve linear regression analysis of both absolute and signed PEs.

Br J Anaesth 2009; **102**: 626–32

Keywords: anaesthetics i.v., propofol; computer simulation; drug delivery, computerized; pharmacokinetics, models; pharmacokinetics, propofol

Accepted for publication: February 9, 2009

The first commercial target-controlled infusion (TCI) devices became available in 1996 and all incorporated the 'Diprifusor' TCI module (AstraZeneca, Macclesfield, UK), which uses the Marsh[1] modification of the pharmacokinetic model described by Gepts and colleagues.[2] (A typographical error occurred in the Marsh publication where the value of k_{12} implemented in Diprifusor software is 0.114 min^{-1} as in the original Gepts paper. In this study all simulations were performed with the 'Diprifusor' model instead of the Marsh model which has k_{12} of 0.112 min^{-1}.) This model was selected for clinical studies, on the basis of simulation studies,[3] as the most accurate of the three models ('Marsh', 'Tackley',[4] and 'Dyck and Shafer'[5] evaluated at that time. The same three models were compared in a clinical study and similar results obtained.[6] By the selection of a single preferred model, the delivery of propofol in any TCI device incorporating the Diprifusor module was standardized in pumps manufactured by different companies. Clinical validation studies with prototype Diprifusor systems provided information on target blood propofol settings for inclusion in propofol ('Diprivan', AstraZeneca) drug labelling, and assessment of predictive performance in two studies[7 8] indicated a degree of positive bias, which was considered clinically acceptable. Diprifusor TCI systems are now widely used in most countries of the world but require the use of an

electronically tagged prefilled syringe of propofol. As less-expensive preparations of propofol have become available, a demand arose for TCI devices that did not require the tagged presentation. Two such systems are the 'Base Primea' (Fresenius Kabi, Brezins, France) and the 'Asena PK' (Cardinal Health, Runcorn, UK). These systems provide the user with a choice of two models for the administration of propofol, the Marsh model or a population model with covariates as described by Schnider and colleagues.[9] As different models may deliver different amounts of propofol, this study was designed to compare the predictive performance of the Diprifusor and Schnider models for propofol. The study was extended to include a recent modification of the Marsh model proposed by White and co-workers,[10] with covariates for age and sex, and another population model described by Schuttler and Ihmsen.[11]

Methods

Computer simulation using the program PK-SIM (Specialized Data Systems, Jenkintown, PA, USA) was used to predict blood propofol concentrations with each pharmacokinetic model. The input profile was that used in an earlier study,[12] which compared the pharmacokinetics of propofol administered as an infusion in patients with cirrhosis and in control patients with normal renal and hepatic function. Of the 10 control patients, this study used data for nine for whom complete patient characteristic information was available. In the clinical study patients had been premedicated orally with diazepam and atropine and anaesthesia induced and maintained using a stepwise infusion of propofol 21 mg kg h^{-1} for 5 min, 12 mg kg h^{-1} for 10 min, and 6 mg kg h^{-1} for the rest of the procedure that lasted for a minimum of 2 h. Small incremental doses of fentanyl (50 μg) were given i.v. as required and the patient's lungs were ventilated to normocapnia with a mixture of 66% nitrous oxide in oxygen. Predicted propofol concentrations obtained by simulation of the propofol infusion scheme used were compared with arterial blood concentrations which had been measured using a standard method[13] at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 30, 40, 50, 60, 75, 90, 105, and 120 min after the beginning of infusion and at 2, 4, 6, 8, 10, 20 min after the end of infusion. A variable number of additional samples were collected when the duration of infusion exceeded 120 min.

The predictive performance of each pharmacokinetic model was assessed using the methodology proposed by Varvel and colleagues.[14] At each time point when a measured blood concentration was available, the PE was calculated as:

$$\mathrm{PE}\,(\%) = \frac{C_\mathrm{m} - C_\mathrm{p}}{C_\mathrm{p}} \times 100$$

where C_m and C_p are the measured and predicted blood concentrations. For each patient, median PE (MDPE) as a measure of bias, and median absolute PE (MDAPE) as a measure of inaccuracy were determined. Values were calculated using all the samples for a given patient and also for the following periods:1–5 min (rapid infusion), 1–21 min (early phase), 25 min to end of infusion (maintenance phase), and 2–20 min after the end of infusion (recovery phase). The variability in PE was characterized by wobble (the median absolute deviation of PE from MDPE). Divergence was calculated in two ways: as the slope of the linear regression of absolute performance error (APE) against time as advocated by Varvel and colleagues and also as the regression of signed PE against time. Median values obtained with the Diprifusor group were compared with values obtained in the other groups with the Wilcoxon signed rank test. Fisher's Exact test was used to compare the proportions of patients in which bias of 20% or less was seen. Linear regression was also used to examine the relationship between the duration of the maintenance infusion and the overall value of divergence, the overall value of MDPE and the MDPE for the maintenance phase obtained for each patient. A value of $P<0.05$ was considered significant. Statistical analysis was performed with the Data Analysis module of Excel (Microsoft) and StatsDirect software (StatsDirect Ltd, Altrincham, UK).

Results

The physical characteristics of the nine patients studied are given in Table 1. The duration of infusion exceeded 120 min in all patients. A total of 286 arterial propofol concentrations were compared with concentrations predicted by each of the four models evaluated at each measurement point. Each patient contributed 29–36 samples with five samples from the rapid infusion phase, 13–15 samples from the early phase, 9–15 from the maintenance phase, and 6–7 from the recovery period. Figure 1 provides an illustration of the inter-patient variability in measured blood propofol concentrations with the standardized infusion scheme used. Among the times shown, the greatest degree of variation was seen at the 5 min time-point.

Table 1 Patient characteristics and duration of propofol infusion. LBM, lean body mass; BMI, body mass index

Patient	Sex	Age (yr)	Body weight (kg)	Height (cm)	LBM (kg)	BMI (kg m^{-2})	Duration of infusion (min)
D1	M	24	60	172	50.4	20.2	142
D2	M	34	55	168	46.8	19.5	226
D8	F	54	55	163	42	20.7	296
H3	M	55	70	172	55.8	23.6	287
H5	M	56	85	170	61.5	29.4	180
H6	F	52	70	172	50.4	23.6	151
W2	M	33	67	172	54.3	22.6	133
W3	M	39	96	184	70.8	28.4	162
W5	F	30	50	150	37.1	22.2	208
Mean		41.9	67.5	169.2	52.1	23.4	198.3
SD		4.13	5.01	3.03	3.37	1.15	3.03