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PHARMACOKINETIC MODEL DRIVEN INFUSION OF PROPOFOL IN CHILDREN

B. MARSH, M. WHITE, N. MORTON AND G. N. C. KENNY

SUMMARY

A computer controlled infusion device for propofol was used to induce and maintain general anaesthesia in 20 children undergoing minor surgical procedures. The device was programmed with an adult pharmacokinetic model for propofol. During and after anaesthesia, blood samples were taken for measurement of propofol concentrations and it was found that the values obtained were systematically over-predicted by the delivery system algorithm. New pharmacokinetic microconstants were derived from our data which reflected more accurately the elimination and distribution of propofol in a prospective study involving another 10 children.

KEY WORDS

Anaesthesia: paediatric. Anaesthetics, intravenous: propofol. Pharmacokinetics: computer model.

The use of i.v. agents to maintain anaesthesia has become increasingly popular since the introduction of propofol. Several manual infusion schemes have been proposed for use in adults, based either on the concept of minimum infusion rate [1] or on approximations to computer generated infusion regimens [2]. Alternatively, delivery may be effected automatically by a pharmacokinetic model driven computer controlled device [3, 4]. This latter approach allows anaesthetic drugs to be administered to a theoretical target plasma concentration calculated mathematically by the delivery system algorithm.

Hitherto, experience with these systems has been confined to adult patients. There is considerable interest in the use of propofol in children, particularly within the context of day-case anaesthesia. Browne, Wolf and Prys-Roberts have proposed recently a manual infusion regimen for paediatric use of propofol and alfentanil [5]. They found the resultant anaesthesia to be satisfactory, providing the increased requirement for propofol in this age group was taken into account. Recent studies of the pharmacokinetic behaviour of propofol after administration of a bolus [6, 7] have suggested a disparity in pharmacokinetic behaviour of the drug between adults and children, which would account for at least part of this increased requirement.

In this study, we report the use in 20 healthy children of a computer controlled infusion system for propofol [4] which used initially an adult pharmacokinetic model described previously. The principal objective of the study was to derive new pharmacokinetic microconstants which more accurately described the elimination and distribution of propofol during infusion anaesthesia in children.

PATIENTS AND METHODS

The infusion system consisted of a Psion II computer interfaced with the Ohmeda 9000 infusion device [8]. We retained the adult three-compartment model used previously [4], describing the pharmacokinetics of propofol [9] with the microconstants of rate of transfer between the three compartments as shown in table I. It was necessary to increase the maximum predicted target plasma concentration of propofol to 15 $\mu g\ ml^{-1}$ (originally 10 $\mu g\ ml^{-1}$ in the adult system). This was to allow for the greater

BRIAN MARSH, M.B., CH.B., F.F.A.R.C.S.I., MARTIN WHITE, B.SC.(HONS), PH.D., M.B., CH.B., F.C.ANAES. (Division of Anaesthetics); GAVIN N. C. KENNY, M.B., CH.B., B.SC.(HONS), M.D., F.C.ANAES. (University Department of Anaesthetics); Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER. NEIL MORTON, M.B., CH.B., F.C.ANAES., Division of Anaesthetics, Royal Hospital for Sick Children, Glasgow.
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Correspondence to M.W.

TABLE I. *Adult pharmacokinetic variables for propofol* [9]. * *Obtained from our own pilot studies*

Vc	228 ml kg^{-1}*
k_{10}	0.119 min^{-1}
k_{12}	0.112 min^{-1}
k_{13}	0.0419 min^{-1}
k_{21}	0.055 min^{-1}
k_{31}	0.0033 min^{-1}

requirement for propofol in children. Adjustments to the pharmacokinetic variables were made solely on the basis of body weight. The Ohmeda 9000 infusion pump was set at a maximum infusion rate of 1200 ml h^{-1}. Precise details of the theoretical blood propofol profile, together with the infusion regimen delivered to each patient, were recorded automatically on the Psion datapacks and these were stored for subsequent computer analysis.

For the first part of the study, we studied 20 children (ages 1–12 yr, ASA grades I or II) presenting for inpatient general surgical or urological procedures (group 1). In the second prospective part of the study, we studied another 10 children (ages 1–9 yr) (group 2). Ethics Committee approval was obtained and written informed consent was given by each patient's parents or guardian.

Anaesthetic technique

Premedication consisted of oral temazepam elixir 0.3 mg kg^{-1} or trimeprazine elixir 2 mg kg^{-1} 1 h before operation. At the same time, EMLA cream was applied under an occlusive dressing to the dorsum of each hand. In the anaesthetic room, a 22-gauge cannula was inserted to a vein in the dorsum of the child's hand and connected to the infusion pump via a 200-cm extension. Immediately before induction of anaesthesia, the child's weight was entered into the Psion, as was the selected theoretical target blood concentration of propofol. Anaesthesia was induced with the pump operating at maximal flow rate (1200 ml h^{-1}), delivering propofol to the desired theoretical target plasma concentration. Anaesthesia was supplemented with 66% nitrous oxide in oxygen via a facemask or laryngeal mask. Analgesia was provided by an appropriate regional nerve block (which consisted of either an ilio–inguinal nerve or caudal block with 0.25% bupivacaine 0.5 ml kg^{-1}). All patients were allowed to breathe spontaneously throughout the procedure and each was monitored with a pulse oximeter, automated non-invasive arterial pressure cuff and electrocardiograph and the quality of anaesthesia was assessed by the supervising anaesthetist according to the presence or absence of either patient movement or cardiorespiratory changes.

Peripheral venous blood samples (maximum 1 ml kg^{-1}) were collected from a large forearm vein on the side of the body contralateral to the site of infusion for measurement of whole blood concentration of propofol according to the method of Plummer [10], the only modification being that the final residuum was analysed by gas–liquid chromatography rather than high pressure liquid chromatography. The between-batch coefficient of variation of the assay was 4.9% at 1 μg ml^{-1} and 2.1% at 10 μg ml^{-1}. The limit of detection was 50 ng ml^{-1}. The calibration graphs were linear over the range 50–20 000 ng ml^{-1}.

During operation, the target blood concentration was adjusted to a value appropriate to maintain adequate anaesthesia as judged clinically by the supervising anaesthetist. At the end of the operation, the infusion pump was switched off and further sampling was perfomed until eye-opening was observed. During this recovery phase, the system continued to calculate theoretical blood concentration.

Computer analysis

Throughout the study, measured blood concentrations of propofol (Cp) were compared with the corresponding delivery system predicted value. The prediction error was calculated for each data point, this being defined as [11, 12]:

$$\text{Prediction error} = \frac{Cp\,(\text{measured}) - Cp\,(\text{predicted})}{Cp\,(\text{predicted})} \times 100$$

Bias is defined as the mean prediction error and is taken in these circumstances to be a measure of the systematic tendency of the system to underestimate the measured concentration of blood propofol. That is to say, if bias has a positive value, then the measured value is, on average, greater than the system prediction and *vice versa*. Precision is defined as the mean value of the sum of individual absolute values of prediction error and is a measure of the degree of scatter of the data about the line of perfect prediction.

Computer analysis of the data for each individual was performed using an iterative

weighted least squares regression program which minimized the total squared prediction error for each patient. In each case, all microconstant systems producing a fit with a consequent value of bias for each individual within 10% were stored on computer disc. The data obtained for the entire population were subjected to a second analysis in which each individual's file of microconstant solutions was applied systematically to all the patient profiles in the study in such a way as to select the microconstant system which was calculated to produce the minimum population bias.

RESULTS

Figure 1 illustrates the course of a typical anaesthetic administered to a 22.5-kg child (aged 7 yr) undergoing herniotomy using the computer aided infusion device. Anaesthesia was induced by selecting an initial theoretical target concentration of 14 μg ml^{-1}. Thereafter, the target could be reduced to 12 μg ml^{-1} without deterioration in the operating conditions, and this target value was maintained for the remainder of the operating time. The anaesthetist retained at all times the option of increasing or decreasing the theoretical target blood concentration according to his or her clinical impression of the quality of anaesthesia. At the termination of surgery, the pump was switched off and the patient transferred to the recovery room, where the device calculated the theoretical decay of propofol concentration in the patient's blood until eye opening was observed. In figure 1, the measured values of blood propofol are overlaid on the system record of the theoretical propofol profile and it can be seen that, in this individual, the delivery system consistently overpredicted the measured blood concentration of propofol.

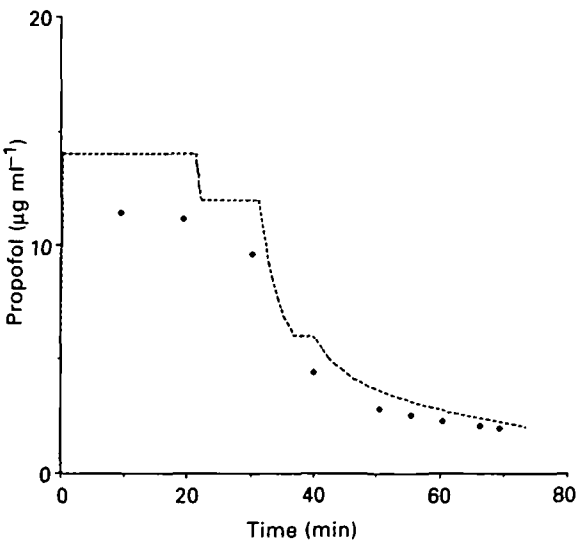

FIG. 1. Predicted and measured blood concentrations of propofol during anaesthesia in a 22.5-kg patient (age 7 yr). The dotted line represents predicted values; individual points are measured values.

TABLE II. *Patient characteristics (mean (SD) [range])*

	Group 1	Group 2
n	20	10
Age (yr)	4.8 [2–10]	4.9 [1–9]
Weight (kg)	18.3 (4.4) [12–28.8]	17.4 (4.9) [12.7–30]

For the population in the first study (table II), each measured blood value of propofol was compared with its corresponding delivery system prediction and the relationship obtained is displayed in figure 2. These results were plotted in the form of percentage error *vs* predicted concentration (fig. 3). It may be seen from this figure that the majority of the data points lie below the line of zero prediction error (the line of perfect prediction). The population mean prediction error (bias) was calculated to be −18.5% and the corresponding value for precision obtained was 25.4%. Hence it was concluded that the delivery device systematically overpredicted the measured values of blood propofol. The most likely reason for this finding is that, compared with adults, children have different pharmacokinetics for handling the drug, and a revised pharmacokinetic model is required to effect more accurate delivery of propofol in the paediatric population under conditions of infusion anaesthesia. In order to derive such a pharmacokinetic model, computer analysis of the data for each individual was performed using the methodology described in the Computer Analysis section.

The microconstant systems which gave the best fit for each individual are detailed in table III. The data obtained for the entire population were then subjected to a second analysis in which each individual's file of microconstant solutions was applied systematically to all the patient profiles in the study in such a way as to select the microconstant system which was calculated to produce the smallest population bias. In this way,

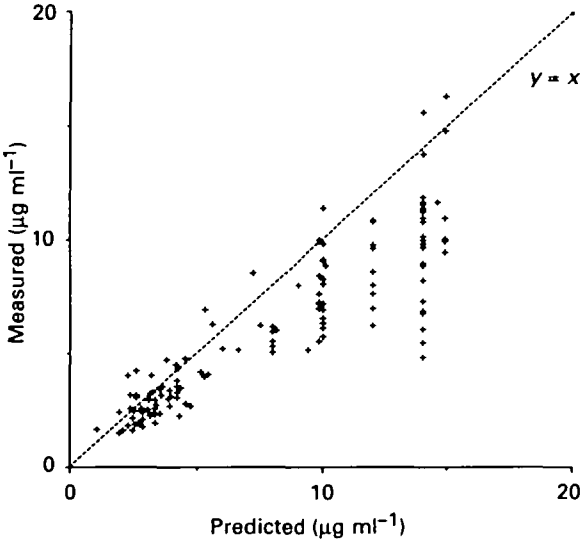

FIG. 2. Comparison of measured and predicted blood concentrations of propofol for the study population. The dashed line is the line of identity ($y = x$).

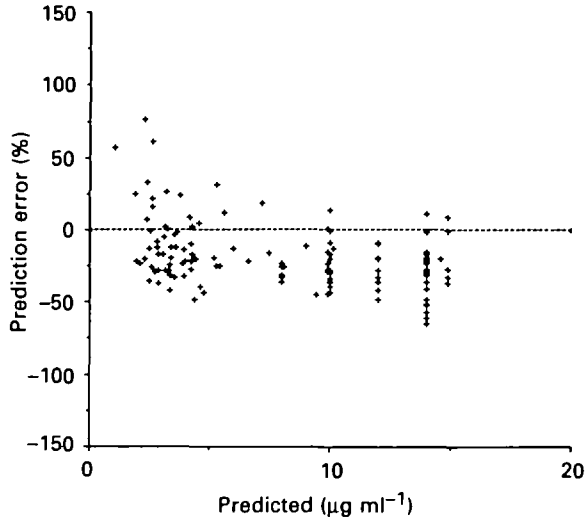

FIG. 3. Comparison of percentage prediction error and predicted values.

a new microconstant system producing a study population bias of 0.9% (precision 20.1%) was recorded (table IV). This value of bias for the new microconstant system is determined on the basis of a new calculated predicted value relating to each experimentally obtained measured blood value. The relationship between each of these new calculated predictions with each of its related measured blood values is displayed in figure 4. In figure 5, each new prediction error is related to its new predicted value. Comparison of this plot with that in figure 3 reveals that the data points are now distributed about the line of zero prediction error (the line of perfect prediction) in such a way that the mean prediction error (bias) is almost zero whereas previously, on the basis of the adult

TABLE III. *Individual best fit pharmacokinetic variables. In all patients* $k_{31} = 0.0033\ min^{-1}$. *The value of* k_{31} *was not iterated in the computer analysis, as simulation revealed that substantial variation of this microconstant made little difference to the prediction obtained and that non-iteration of* k_{31} *decreased the program run greatly to acceptable times*

Patient no.	Age (yr)	Weight (kg)	Vc (ml kg^{-1})	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{21} (min^{-1})
1	5	21.6	343	0.08	0.085	0.042	0.03
2	5	18	371	0.12	0.114	0.021	0.08
3	7	20	314	0.10	0.17	0.021	0.04
4	10	25.6	257	0.08	0.17	0.021	0.04
5	4	16.6	371	0.1	0.114	0.042	0.04
6	7	22.5	371	0.08	0.085	0.031	0.03
7	3	15.2	343	0.1	0.057	0.021	0.04
8	5	16.2	371	0.12	0.057	0.021	0.03
9	3	15.8	343	0.08	0.142	0.021	0.03
10	2	14.5	257	0.1	0.17	0.031	0.04
11	2	12	343	0.16	0.17	0.042	0.05
12	4	20	343	0.1	0.17	0.042	0.05
13	7	28.8	371	0.08	0.142	0.031	0.03
14	5	21	286	0.14	0.114	0.063	0.05
15	9	17.5	343	0.12	0.142	0.05	0.07
16	3	16.2	343	0.08	0.057	0.021	0.03
17	3	12.7	343	0.18	0.171	0.021	0.08
18	4	15.7	371	0.08	0.085	0.063	0.05

TABLE IV. *Derived pharmacokinetic microconstants for paediatric population (group 1), and comparison of bias and precision (95% confidence limits) obtained by computer simulation using these microconstants with values obtained experimentally using the adult pharmacokinetic delivery system*

Derived microconstant		Bias (%)	Precision (%)
Vc	343 ml kg^{-1}	Adult system	
k_{10}	0.1 min^{-1}	−18.5 (−14.8 to −22.6)	25.4 (22.8–27.8)
k_{12}	0.0855 min^{-1}		
k_{13}	0.021 min^{-1}	Paediatric simulation	
k_{21}	0.033 min^{-1}	0.9 (−4 to 5.7)	20.1 (17.6–24.2)
k_{31}	0.0033 min^{-1}		

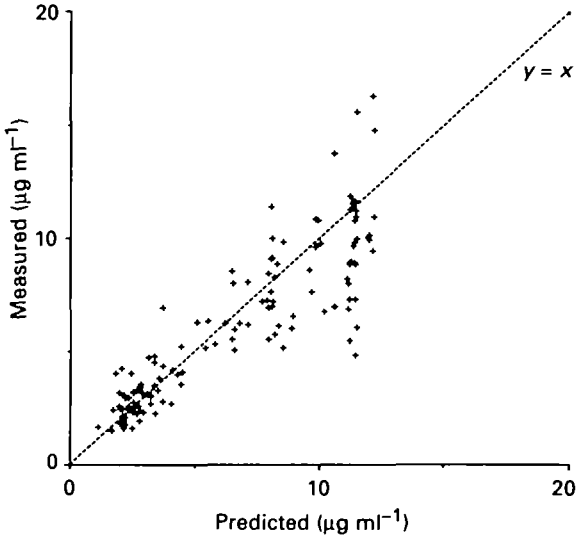

FIG. 4. Comparison of measured and predicted blood concentrations of propofol for the study population. The predicted values are derived by pharmacokinetic simulation using the derived paediatric pharmacokinetic parameters for propofol. Dotted line represents the line of identity ($y = x$).

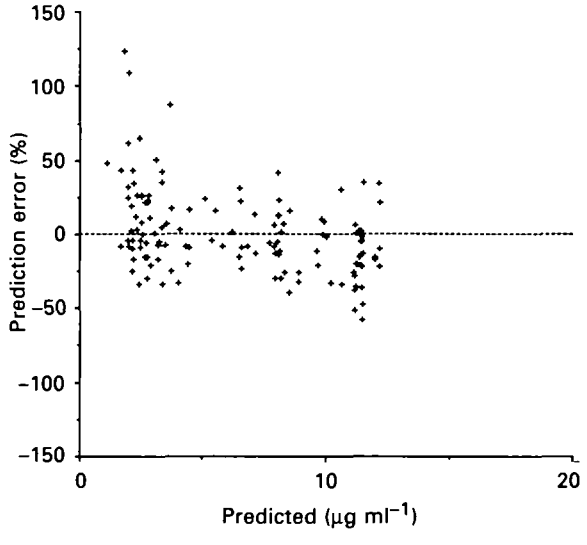

FIG. 5. Comparison of percentage prediction error and new predicted values obtained by pharmacokinetic simulation using the derived paediatric pharmacokinetic parameters for propofol.

pharmacokinetic model, the data points generally tended to lie well below the line (resulting in negative bias). In figure 6, a pharmacokinetic simulation program has been used to predict the effect (using the new pharmacokinetic model) on blood concentration of propofol of the infusion regimen administered to the patient referred to in figure 1. The infusion regimen is a function of the adult pharmacokinetic microconstants used in the original delivery system and the postulated patient model, into which the drug is delivered, is governed by the new derived microconstants detailed in table IV. The new computer prediction has been overlayed on the data displayed in figure 1. It can be seen from this figure that the new paediatric pharmacokinetic model produces a predicted concentration profile for propofol that fits more closely the measured blood values obtained for this particular patient.

In order to test the new paediatric pharmacokinetic model prospectively, a second study was performed in the patients in group 2 (table II). In this second study, the computer controlled propofol infusion system was programmed with the revised paediatric microconstants. As before, measured blood concentrations of propofol were compared with their corresponding predicted values calculated by the delivery system algorithm. Figure 7 shows the relationship between measured and predicted values for the entire prospective study population and figure 8 shows the distribution of prediction errors in relation to their predicted values. The bias of the revised

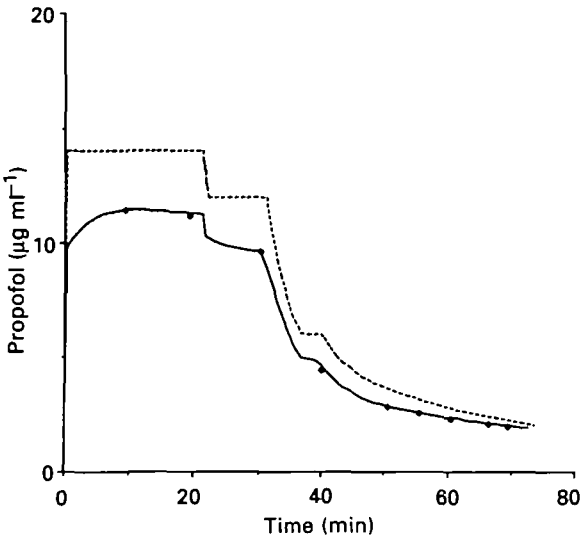

FIG. 6. Predicted and measured blood concentrations of propofol for the patient referred to in figure 1, the predicted values in this case calculated by computer pharmacokinetic simulation using the derived paediatric parameters. The computer generated profile (solid line) is superimposed on figure 1.

delivery system was calculated to be 2.8% and the corresponding value of precision was 16.2%. It can be seen that, prospectively, the revised paediatric microconstant system gave a relationship between measured and predicted values of blood propofol which was superior to that obtained using the adult microconstant system used in the initial study and which compared closely to the relationship predicted by computer simulation using the revised paediatric microconstant system.

DISCUSSION

In this report, we have described the use of a computer controlled propofol infusion device to maintain general anaesthesia in a population of children undergoing minor general surgical procedures. At the commencement of this study, no information was available describing the pharmacokinetics of propofol in young children. The device was therefore programmed with adult pharmacokinetic microconstants and it was observed that the theoretical blood concentration of propofol was attained only rarely on direct measurement of drug concentration in the patients' blood. The delivery device was observed to overpredict systematically the measured blood concentration of propofol (bias = −18.5%). The major objective of this study was to derive from

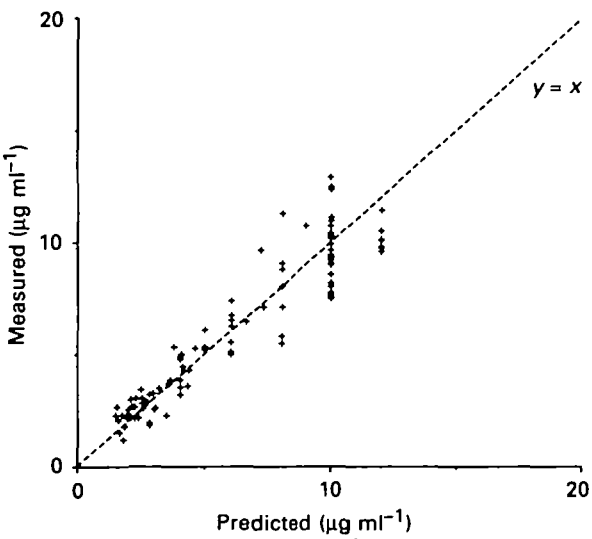

FIG. 7. Comparison of measured and predicted values for the prospective study population (group 2). The computerized infusion system was programmed with the revised paediatric microconstant system. Dotted line represents the line of identity ($y = x$).

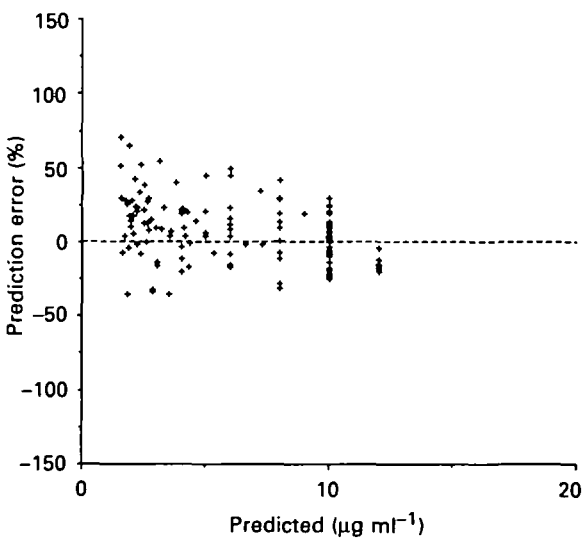

FIG. 8. Comparison of percentage prediction error and predicted values of blood concentrations of propofol corresponding to the data presented in figure 7. Dotted line represents the line of zero prediction error.

TABLE V. *Pharmacokinetic variables for propofol derived after the administration of a single dose [6]*

Vc	722 ml kg^{-1}
k_{10}	0.0509 min^{-1}
k_{12}	0.112 min^{-1}
k_{13}	0.0195 min^{-1}
k_{21}	0.0454 min^{-1}
k_{31}	0.00143 min^{-1}

these measurements of blood propofol a new set of pharmacokinetic microconstants which more accurately describes the elimination and distribution of the drug in children during infusion anaesthesia (bias = 0.9%) (table IV). The derived paediatric pharmacokinetic system was tested prospectively in a second study population and this resulted in a bias of 2.8%.

The precision calculated when the revised pharmacokinetic microconstants are applied to the data in group 1 was 20.1%, which differs little from the value obtained originally when the adult system was applied. Indeed, it proved impossible by computer modelling to construct a single pharmacokinetic model for the study population which resulted in a precision of much less than this value. In the prospective study, a value for precision of 16.2% was obtained. It is likely that the observed values of precision that we have obtained are a consequence of heterogeneity of pharmacokinetic handling within our study populations and that precision could be improved only by creating multiple models within the study population to account for pharmacokinetic variability.

The volume of the central compartment (Vc) of the new paediatric model was calculated to be 343 ml kg^{-1}, which is approximately 50% greater than the value used in the adult pharmacokinetic model (228 ml kg^{-1}). The clearance of the drug, which is the product of Vc and k_{10}, is calculated to be 34.30 ml kg min^{-1}, compared with an adult value of 27.36 ml kg min^{-1}.

Saint-Maurice and colleagues [6] have reported information on the pharmacokinetic behaviour of propofol in a population of 10 children, aged 4–7 yr, based on the administration of a bolus dose of propofol at induction (table V). They reported a substantially greater value for Vc in children (722 ml kg^{-1}) compared with adults, but a broadly similar value of clearance (30.6 ml kg^{-1} min^{-1}). We used a pharmacokinetic simulation program to test the response of Saint-Maurice's microconstant system to the infusion profiles delivered to the patients in our study. We found that this microconstant system systematically underpredicted the measured values of blood propofol obtained from the patients in our study (bias = 33.9% (95% confidence limits (CL) 27.1–40.6); precision = 40% (95% CL 35.3–46.4). We concluded, therefore, that the microconstants derived by Saint-Maurice and colleagues were unsuitable for describing the elimination and distribution of propofol in children during infusion anaesthesia. It is possible that this result derives from the difficulty in describing the initial distribution phase of the drug following bolus administration, because of the effects of inadequate mixing immediately after administration and because of difficulties inherent in the necessity for rapid sampling [13, 14].

It was found during the course of this study that substantially greater theoretical target concentrations of propofol were required to maintain adequate anaesthesia in children than observed previously in the adult population [4]. It was frequently necessary to achieve a theoretical target concentration of 14 μg ml^{-1} in order to achieve satisfactory induction, whereas in adults a theoretical target of 4–6 μg ml^{-1} was usually adequate. This discrepancy is explained in part by the differences in propofol pharmacokinetics of the two populations and in part by the consideration that no opioid agent was used in our paediatric study, analgesia being provided instead by a local block.

The principal consequences for an infusion scheme using our newly derived paediatric pharmacokinetic microconstant system for propofol are that, for a given target, the size of the initial loading bolus is increased by approximately 50% compared with the adult system and the maintenance infusion thereafter is increased by approximately 25% at equilibrium.

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