A prospective evaluation of pharmacokinetic model controlled infusion of propofol in paediatric patients

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SUMMARY

We have tested a published algorithm for pharmacokinetic model controlled infusion of propofol to supplement 67% nitrous oxide for general anaesthesia in Chinese children aged 4-10 yr. Initially we studied 10 children undergoing minor procedures with spontaneous ventilation; mean duration of surgery was 38 min and mean propofol infusion rate 497 μg kg⁻¹ min⁻¹. The precision of the model was 24.8% and bias -18.5%. The model was revised using an iterative linear least squares regression procedure and the revised model tested prospectively in another 20 children. The precision of the revised model was 21.5% (range in individuals 8.4-43.1%) and bias -0.1% (range -30 to 42%). Mean propofol infusion rate required to maintain anaesthesia was 474 μg kg⁻¹ min⁻¹ (range 125-737 μg kg⁻¹ min⁻¹). The mean blood concentration required for satisfactory anaesthesia was 6.6 μg ml⁻¹ (range 3-11 μg ml⁻¹) and the mean blood concentration at the time of waking, which occurred 40 min after switching off the infusion, 0.86 μg ml⁻¹ (range 0.40-1.45 μg ml⁻¹). Our patient population required different pharmacokinetic variables from those in the previous study. Recovery was slow because of the high infusion rates required to maintain satisfactory anaesthesia and large difference between the blood concentration required for anaesthesia and that at which waking occurred. (Br. J. Anaesth. 1994; 72: 302-306)

KEY WORDS

The concept of computer controlled infusion devices to deliver i.v. anaesthetic drugs according to pharmacokinetic model-driven algorithms is attractive. Drugs may be administered to a theoretical blood concentration calculated by the algorithm. All relevant pharmacokinetic data are contained in the algorithm implying that administration of the infusion is simplified and there is no need to remember formulae for delivering the infusion by manual adjustment. The blood concentration–time curve calculated by the computer also gives an indication of likely recovery times after discontinuing the infusion. However, successful use of these algorithms requires a knowledge of blood concentration–effect relationships for the drug and of the accuracy of the algorithm.

In this study we tested prospectively the use of an algorithm published previously for administering propofol to paediatric patients [1]. The objectives of the study were to test the accuracy of the algorithm in our patient population, determine the minimum infusion rate required for satisfactory anaesthesia and compare times for recovery from the anaesthetic with predicted blood concentrations using the model.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed consent was obtained from the children’s parents. We studied patients aged 4-10 yr, all were healthy (ASA I), had been full-term babies, had no contraindications to the drugs used in the trial and were undergoing minor surgical procedures associated with minimal blood loss. Patients with a haemoglobin concentration of less than 11.5 g dl⁻¹ before operation were excluded because of the need to take multiple blood samples. EMLA cream 5% (2.5% lignocaine and 2.5% prilocaine, Astra Pharmaceuticals, Sweden) was applied to the dorsum of one hand 1 h before operation to assist with placement of the i.v. catheter. Anaesthesia was induced with i.v. propofol by an infusion pump and maintained using the propofol infusion and 70% nitrous oxide in oxygen. All patients breathed spontaneously.

The study was conducted in two parts. In the first part we studied 10 patients to determine the accuracy of the algorithm in our population. For the first patient, the initial blood concentration chosen was propofol 10 μg ml⁻¹. This initial blood concentration was then adjusted, up or down, by 2 μg ml⁻¹ for each subsequent patient, according to whether or not the previous patient moved or did not move in response to surgical incision, which was made at 5-10 min after induction of anaesthesia. Postoperative analgesia was provided at the end of the procedure using 0.25% bupivacaine (maximum...
2.0 mg kg\(^{-1}\)) by either direct infiltration into the operation site by the surgeon or local nerve block performed by the anaesthetist. The target concentration of propofol was adjusted to maintain a satisfactory depth of anaesthesia according to standard clinical criteria, including movement in response to pain, ventilatory, cardiovascular and sympathetic nervous system signs. Time from switching off the infusion until eye opening in response to verbal command was recorded.

After analysis of the results of the first part of the study, the accuracy of the pharmacokinetic algorithm was improved using an iterative linear least squares regression program. Another 20 patients were then studied to test prospectively the accuracy of the revised pharmacokinetic model. These patients were also part of a comparative study of recovery in paediatric patients undergoing minor elective surgery using a variety of anaesthetic techniques [2]. The anaesthetic technique was identical to that used in the first part of the study except that the initial blood concentration was always 8 μg ml\(^{-1}\) and the local anaesthetic block was performed before commencing surgery. The initial blood concentration of 8 μg ml\(^{-1}\) was equivalent to a bolus dose of propofol 3.5 mg kg\(^{-1}\).

The propofol infusion model used was similar to that of Marsh and colleagues [1]. The system consisted of an Ohmeda 9000 syringe pump (Medishield, U.K.) controlled by a 386SX IBM compatible lap-top computer via an RS232C serial interface. After purging the i.v. tubing using the purge option on the pump, an initial bolus of propofol 10 mg ml\(^{-1}\) was given according to body weight at the top rate of the pump (1200 ml h\(^{-1}\)). Blood concentration was adjusted, up or down, in 0.05 mg ml\(^{-1}\) steps, as required.

When the patient was asleep, a second i.v. cannula was placed in a large vein in the limb opposite to that used for the propofol infusion. This was used for obtaining venous blood samples for later analysis of blood concentrations of propofol. Blood samples were obtained at the time of surgical incision and at 5–10-min intervals throughout the procedure. Up to five samples were obtained also in the recovery room during the first 2 h after termination of the infusion. A minimum of 12 2-ml blood samples were obtained from each patient. Blood samples were stored at 4 °C for later analysis.

Whole blood concentrations of propofol (C\(_p\)) were measured by high pressure liquid chromatography with fluorescence detection [3]. All analyses were performed within 1 month of specimen collection, a time during which there is no decay in whole blood concentrations of propofol. The between-batch coefficient of variation of the assay was 6.7% at 50 ng ml\(^{-1}\) and 4.0% at 3000 ng ml\(^{-1}\). The limit of detection of the assay was 2 μg ml\(^{-1}\). Calibration graphs were linear over the range 2000–3000 ng ml\(^{-1}\). For specimens with expected concentrations of propofol greater than 3000 ng ml\(^{-1}\), dilution was used to decrease propofol concentration to within the calibrated range of the assay.

Prediction error of the model was calculated as: prediction error = \((C_p\text{ (measured)} - C_p\text{ (predicted)})/C_p\text{ (predicted)}\) \(\times 100\). Bias was defined as the mean prediction error and precision as the mean of the absolute values of the prediction error [1]. Bias and precision were calculated for each patient and the overall mean values calculated. For patients in the second phase of the study, precision during the infusion phase was calculated also for each individual about that individual's bias during the infusion phase to examine the ability of the infusion model to maintain a constant blood concentration. This procedure was not performed for patients in the first phase of the study because of the small number of patients studied and the small number of blood samples obtained. An iterative linear least squares regression program written by one of the authors (Y.H.T.), which minimized the total squared prediction error for each patient, was performed to find revised rate constants that would best fit the study population. The mean squared errors for each patient before and after least squares regression were compared using a paired \(t\) test. Time to eye opening on command was compared with duration of infusion using linear correlation. The computer software package Statview II (Abacus Concepts Inc, Berkeley, U.S.A.) was used to perform these tests. A value of \(P < 0.05\) was regarded as significant.

**RESULTS**

The characteristics of the patients studied in the two phases of the study are shown in table I. Operations performed included inguinal herniotomy, circumcision, orchidopexy and excision of subdermal cyst.

In the first part of the study, 67 blood samples were obtained from the 10 patients. The mean total dose of propofol administered was 372 mg (range 263–563 mg) and the mean rate of infusion was 497 μg kg\(^{-1}\) min\(^{-1}\) (225–776 μg kg\(^{-1}\) min\(^{-1}\)). Blood concentrations for maintaining satisfactory anaesthesia ranged from 5 to 13 μg ml\(^{-1}\). The precision of the model was 24.8% and bias -18.5%. After the iterative linear least squares regression procedure, the revised pharmacokinetic variables had a theoretical precision of 23.1% and bias of -0.3% (table...
TABLE II. Comparisons of initial and revised rate constants for propofol using a three-compartment open model for patients in the first part of the study and prospective evaluation of the revised rate constants. Numbers in parentheses are range for individual patients. The revised model fitted the data significantly better than the initial model (P < 0.001). \( V_c = \) Central volume of distribution.

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Revision 1</th>
<th>Prospective testing of Revision 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_c ) (ml kg(^{-1}))</td>
<td>343</td>
<td>432</td>
<td>432</td>
</tr>
<tr>
<td>( k_{10} ) (min(^{-1}))</td>
<td>0.1</td>
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<td>0.0967</td>
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<tr>
<td>( k_{12} ) (min(^{-1}))</td>
<td>0.0855</td>
<td>0.1413</td>
<td>0.1413</td>
</tr>
<tr>
<td>( k_{21} ) (min(^{-1}))</td>
<td>0.021</td>
<td>0.0392</td>
<td>0.0392</td>
</tr>
<tr>
<td>( k_{31} ) (min(^{-1}))</td>
<td>0.033</td>
<td>0.1092</td>
<td>0.1092</td>
</tr>
<tr>
<td>Bias (%)</td>
<td>-18.5 (-41.2-10.4)</td>
<td>-0.3 (-28.9-28.6)</td>
<td>-0.1 (-30-42)</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>24.8 (6.5-41.2)</td>
<td>23.1 (8.2-31.8)</td>
<td>21.5 (8.4-43.1)</td>
</tr>
<tr>
<td>Precision in individuals during infusion phase</td>
<td>11.9 (3.2-30.1)</td>
<td></td>
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</tr>
</tbody>
</table>

![Fig. 1. Correlation between predicted and measured blood concentrations of propofol (\( n = 177, \) \( r = 0.86 \)).](image1)

![Fig. 2. Comparison between predicted blood concentrations of propofol and prediction error (\( n = 177 \)).](image2)

II). Fit of the model was improved significantly (\( P < 0.001 \)). Mean time to eye opening on command after cessation of infusion was 35 min (19-68 min).

During the second phase of the study, 177 blood samples were obtained from the 20 patients. Mean duration of surgery was 32 min (16-65 min) and mean propofol infusion rate 474 \( \mu \)g kg\(^{-1}\) min\(^{-1}\) (125-737 \( \mu \)g kg\(^{-1}\) min\(^{-1}\)). The mean blood concentration for maintaining satisfactory anaesthesia during the infusion phase was 6.6 \( \mu \)g ml\(^{-1}\) (3-11 \( \mu \)g ml\(^{-1}\)) and the mean total dose of propofol administered was 409 mg (222-797 mg).

Precision of the revised model was 21.5% and bias —0.1% (table II). The correlation between measured and predicted concentrations of propofol is displayed in figure 1 and the relationship between blood concentration and prediction error is shown in figure 2. Precision in individuals during the infusion phase was 11.9%. This indicates that the model was better at maintaining a constant blood concentration than at predicting what that blood concentration would be. Further iterative linear least squares regression of the pharmacokinetic variables did not result in a further theoretical improvement in bias or precision of the model.

Mean time to eye opening on command after discontinuing the infusion and nitrous oxide was 40 min (17-80 min) and did not correlate with duration of infusion (\( r = -0.2, \) \( P = 0.2 \)). Predicted blood concentration at this time was 0.86 \( \mu \)g ml\(^{-1}\) (0.40-1.45 \( \mu \)g ml\(^{-1}\)). Four patients had an increase in blood concentration of propofol in the last blood sample, obtained at 52-103 min after cessation of the infusion. The magnitude of the increase was between 7 and 21% and occurred at blood concentrations between 0.83 and 2.50 \( \mu \)g ml\(^{-1}\).

DISCUSSION

In this study we have evaluated prospectively a pharmacokinetic model-driven infusion of propofol based on that of Marsh and colleagues [1]. This model had been developed using children of similar age and undergoing similar procedures to the patients in this study. Its accuracy had been confirmed by prospective testing. When compared with their data, in our patients the precision of the model was lower (24.8% vs 20.1%) and there was a large negative bias; the algorithm underestimated blood concentrations by 18.5%. This indicated that...
the pharmacokinetic data of Marsh and colleagues were not applicable to our patients. Therefore, we revised the pharmacokinetic variables and tested the new variables prospectively, when they were found to fit our population well. This confirms the difference in the pharmacokinetic profiles of the children in the two studies.

The reasons for the difference in pharmacokinetic variables between the present study and that of Marsh and colleagues [1] are unclear. The main differences between the two studies were that our study was of Chinese children and our anaesthetic technique did not include sedative premedication. Analgesia in the form of a local anaesthetic block was also performed at the end of surgery rather than at the beginning, in the first phase of the study. However, although the change to performing the local anaesthetic block before surgery for the second part of the study reduced propofol requirements, it did not alter significantly the pharmacokinetic profile of propofol. The volume of distribution of the central compartment in our model was 25% larger than that of Marsh and colleagues and is close to the value obtained in a previous pharmacokinetic study of a bolus dose of propofol in Chinese children [4]. However, caution must be exercised in interpreting the pharmacokinetic variables in the model after it has been subjected to an iterative least squares regression procedure, because the relative contribution of each variable to the overall model is influenced by its order in the regression procedure. The revised model is regarded best as a mathematical algorithm that best fits the blood concentration-time profile of the drug, rather than a true compartmental pharmacokinetic model.

The large infusion rates required for satisfactory anaesthesia in the first part of the study, when no local anaesthetic block had been performed, caused concern. The mean infusion rate of 499 μg kg⁻¹ min⁻¹ was 40% greater than the ED₉₀ of 348 μg kg⁻¹ min⁻¹ in adult patients who had been premedicated with lorazepam [5]. The Intralipid load at this infusion rate was 0.3 g kg⁻¹ h⁻¹ and in some patients approached the recommended maximum infusion rate for Intralipid of 0.5 g kg⁻¹ h⁻¹. We would recommend the 20 mg ml⁻¹ solution available recently when using this technique for prolonged infusions.

Initial recovery was slow after cessation of the infusion; mean time to eye opening on command was 40 min after discontinuing the infusion and nitrous oxide [2]. The reasons for the slow recovery include the more than seven-fold difference between the mean concentration required to maintain anaesthesia (6.6 μg ml⁻¹) and the mean concentration at which eye opening to command occurred (0.86 μg ml⁻¹) and the large infusion rates required to maintain a constant blood concentration which caused significant accumulation of the drug in the body. The decay in blood concentration after cessation of the infusion was prolonged, even after these brief surgical procedures. Modelling of the decay curve of blood propofol concentration using mean data from the second part of this study demonstrates this point (fig. 3). A bolus dose which attains a blood concentration of 6.6 μg ml⁻¹ (2.85 mg kg⁻¹) and infusions to maintain blood concentrations at 6.6 μg ml⁻¹ for 30 min and 1 h are shown in figure 3. A blood concentration of propofol of 6.6 μg kg⁻¹ was chosen because it was the mean blood concentration required during the infusion phase of the study.

The large infusion rates in the first part of the study (mean infusion rate 497 μg kg⁻¹ min⁻¹) were reduced only slightly by performing the local anaesthetic block before commencing surgery (mean infusion rate 474 μg kg⁻¹ min⁻¹). We are unsure as to why there was not a greater reduction in mean infusion rate in the second part of the study. The most likely explanation is that surgery commenced immediately after performance of the local anaesthetic block, whereas the block may have taken up to 15 min to be effective. A large part of the propofol dose would have been administered already by this time. In addition to waiting for the local anaesthetic block to be effective, it is possible that the infusion rates required for satisfactory anaesthesia could be reduced further and the recovery profile improved, if patients were also premedicated and opioid supplementation was given during operation. The mean concentration of 0.86 μg ml⁻¹ at which eye opening occurred was similar to the concentration of 1.1 μg ml⁻¹ for waking found in adult patients by Shafer and colleagues [6].

We observed the occurrence of a second peak in four patients. This may have been observed in more patients if sampling had been performed later than 1 h into the recovery phase in all patients. Sampling was performed only early in the recovery period because of concern over the number of blood samples obtained and because our objective was to study the accuracy of the algorithm during the infusion and early recovery phases. These were times when patients were sedated markedly and the model was not tested to see if it described fully the elimination of propofol from blood. It is noteworthy that the blood concentrations at which this second peak

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**Fig. 3.** Modelling of the decay in blood concentration of propofol after cessation of an infusion to maintain a constant blood concentration of 6.6 μg ml⁻¹ for 30 min and 60 min, and of a bolus dose which may attain this blood concentration (2.85 mg kg⁻¹). The dashed lines correspond to the mean blood concentration of propofol required to maintain satisfactory anaesthesia and that at which eye opening to command occurred.
occurred exceeded the concentration for eye opening to command. This indicates that there is a need for prolonged observation of these patients and a possibility that clinically significant residual could occur. Second peaks after bolus doses of propofol in children have been described previously at 3 and 12 h after administration of the drug [4].

REFERENCES