Pharmacokinetics of a single bolus of propofol in Chinese children of different ages

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Aims & Objectives
1. To determine a complete PK profile of a single dose of propofol in different aged Chinese children ranging from 4 months to 9 years old.
2. To provide further evidence to support the use of propofol for induction in children younger than 3 years old.
3. To build and use PK models that can accurately describe propofol concentrations in the target population.
4. To establish the population PK parameters and investigate covariate models for prediction of typical parameters in an individual before concentration measurements are available.

Materials and Methods
Study Design
The clinical work was undertaken at the 2nd affiliated hospital of WenZhou Medical College. Thirty-five paediatric patients undergoing general or urinary surgery for congenital megacolon, urinary tract defects or bilateral undescended testes were recruited between February and September 2002. Propofol was administered intravenously. Arterial blood samples were taken at 2, 4, 6, 8, 10, 20, 30, 45, 60, 90, 120, 180 min after propofol injection. For full details please see ShangGuan et al.

Table I – Patient Demographics

<table>
<thead>
<tr>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.4 (0.3-2.8)</td>
<td>9.7 (0.7-14)</td>
</tr>
<tr>
<td>12</td>
<td>3.5 (3.5-5)</td>
<td>13.6 (12.6-18)</td>
</tr>
<tr>
<td>11</td>
<td>6.8 (5-9)</td>
<td>18.5 (12-24)</td>
</tr>
</tbody>
</table>

Table II – Model Building, where *is the final model

<table>
<thead>
<tr>
<th>Model</th>
<th>Objective function value</th>
<th>No. of Structural Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base 1 comp No covariates</td>
<td>-1092</td>
<td>4</td>
</tr>
<tr>
<td>Base 2 comp No covariates</td>
<td>-1356</td>
<td>6</td>
</tr>
<tr>
<td>Base 3 comp No covariates</td>
<td>-1289</td>
<td>6</td>
</tr>
<tr>
<td>Base comp wt age</td>
<td>-1359</td>
<td>8</td>
</tr>
<tr>
<td>Base comp group</td>
<td>-1362</td>
<td>12</td>
</tr>
</tbody>
</table>

When covariate models were applied, weight was found to be a significant covariate for the clearance and volume of distribution parameters. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight had been taken into account, as demonstrated by the marginal drop in objective function value (Table II).

Materials and Methods

Pharmacokinetic Analysis
Population parameter values were estimated using NONMEM. One and three compartment pharmacokinetic models were fitted to the data using subroutines from the NONMEM library (ADVAN1 TRANS2, ADVAN3 TRANS4 and ADVAN1 TRANS3 respectively). The parameters of central (CL_i) and peripheral (V_i) compartment volumes, total body clearance (CL), inter-compartmental clearance between central and peripheral (Q_i), and inter-compartmental clearance between central and peripheral (2Q_i) were estimated for the three compartment pharmacokinetic model.

Clearance Model
- \( CL_i = CL_{GRP} \cdot e^{PPV_{CL}} \)
- \( CL_{GRP} = CL \cdot F_{W/TCL} \)
- \( F_{W/TCL} = \left( \frac{WT}{WT_{STD}} \right)^{\alpha} \)

Volume Model
- \( V_i = V_{GRP} \cdot e^{PPV_{V}} \)
- \( V_{GRP} = V \cdot F_{W} \)
- \( F_{W} = \frac{WT}{WT_{STD}} \)

PPV_i was assumed to be a normally distributed random variable with mean 0
CL_{GRP} is the covariate predicted group value for Clearance
CL_i is the individual Clearance for the i patient
V_i is the predicted propofol concentration (without residual error)

Error Model
- \( Y = F \cdot e^{ERR(1)} \)

F is the individual prediction (without residual error)
Y is the individual prediction including a proportional (ERR(1)) residual error component.
ERR(1) was assumed to be a normally distributed random variable with mean 0
A combined proportional and additive error model was originally applied but the additive error was found to be minimal.

Computation
Model building was performed using NONMEM version V release 1.1 (NONMEM Project Group, University of California, San Francisco, CA, USA) under MS-DOS on a Pentium 4 3GHz PC using Microsoft windows XP and the g77 FORTRAN compiler. All model building was performed using the first order conditional estimation method with the interaction estimation option.

Discussion and Results

All 35 children completed the study. Table 2 describes the model building process undertaken to arrive at the final model for propofol pharmacokinetics in this study. A three-compartment pharmacokinetic model using weight as a covariate on clearance and volume parameters best described the pharmacokinetics of propofol in the study population. Table 3 shows the parameter estimates of the final pharmacokinetic model which included an allometric weight model. The model was applied to standardise the pharmacokinetic parameters using a standard weight of 13.7 kg. The context sensitive half-life was 28 minutes calculated by interpolation. The table also shows the between subject variability on the structural parameters of the model.

Table III – Final Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (95%CI)</th>
<th>BSV^1 (SE(CV)^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_i (L/min 13.7kg^-1)</td>
<td>0.185 (0.137 - 0.233)</td>
<td>0.658 (0.131)</td>
</tr>
<tr>
<td>CL_i (L/min 13.7kg^-1)</td>
<td>54.6 (46.6 - 62.6)</td>
<td>0.142 (0.073)</td>
</tr>
<tr>
<td>V_i (L 13.7kg^-1)</td>
<td>7.2 (5.328 - 9.072)</td>
<td>0.451 (0.136)</td>
</tr>
<tr>
<td>V_i (L 13.7kg^-1)</td>
<td>0.314 (0.064 - 0.685)</td>
<td>0.348 (0.081)</td>
</tr>
<tr>
<td>V_i (L 13.7kg^-1)</td>
<td>0.093 (0.055 - 0.248)</td>
<td>0.049 (0.097)</td>
</tr>
<tr>
<td>Proportional error</td>
<td>0.084 (0.012 - 0.053)</td>
<td></td>
</tr>
<tr>
<td>Time (1/2) (min)</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td>Time (1/2) (min)</td>
<td>14.89</td>
<td></td>
</tr>
<tr>
<td>Time (1/2) (min)</td>
<td>310.8</td>
<td></td>
</tr>
</tbody>
</table>

- ^1 BSV expressed as an approximate CV, ^2 SE expressed as a CV of the BSV term, ^3 SE expressed as a CV of the proportional error

Simulation
Simulation of a 1 hour operation based on the propofol regimen described in the British National Formulary was performed using the final population pharmacokinetic model in NONMEM (Fig 4). The simulation was based on a 1% injection and an initial infusion of 3 mg/kg over 30 seconds. The maintenance infusion was at 12 mg/kg/h. The average weight for each of the groups A and B was used and one thousand replicates run. The generally accepted target concentration of around 4 mg/L is achieved in all groups but not by all individuals.

Conclusions
A three compartment pharmacokinetic model adequately described the pharmacokinetics of propofol in Chinese children aged between 4 months and 9 years.

References

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Fig. 1
Mean Concentration time profile for the three age groups with standard deviation bars

Fig. 2
Measured data with the population predicted fit from the final model with covariates and the corresponding 90% prediction interval

Fig. 3
Individual predicted clearance for the final model vs. weight. Dashed line is the covariate model for the dependence of clearance on weight determined in the final model and the solid line represents the 95% prediction interval. The prediction interval is the clearance range for a given weight based on the between subject variability

Fig. 4
Top left Panel simulation based on the mean weight of the children in group A of the study, 9.7 kg. Lower left panel simulation based on the mean weight of the children in group C of the study, 13.8 kg. The solid lines represent the 95% prediction interval and the dashed purple line is the population prediction

Limitations
The children were premedicated with ketamine, and then anaesthetised using various other medications, e.g. midazolam, fentanyl and diazepam. Pharmacokinetics of propofol can be markedly influenced by drug interactions. However drug interactions should not affect consistency of pharmacokinetics of propofol across the population age when the children were anaesthetised with standardised anaesthetic techniques. There were only two female subjects in the study, thus eliminating the ability to draw conclusions about the effect of sex on the pharmacokinetics.