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. Provide further evidence to support the use of propofol for induction in children younger than 3 years old.
3. Build and use PK models that can accurately describe propofol concentrations in the target population.
4. 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

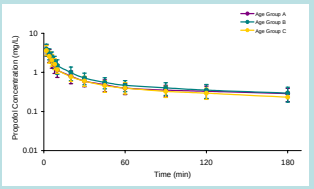
The clinical work was undertaken at the 2nd affiliated hospital of WenZhou Medical College. Thirty-five paediatric patients undergoing general or urinary surgery for congenital megacolon, urinary track defects or bilateral undescended testis were recruited between February and September 2002. Propofol 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 el[1].

Table I – Patient Demographics

	Group A	Group B	Group C
n	12	12	11
Sex (M/F)	12/0	11/1	10/1
Age (years)	1.4 (0.3-2.8)	3.5 (3-5)	6.8 (5-9)
Weight (kg)	9.7 (6-14)	13.6 (12-16)	18.5 (12-24)

Fig. 1

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



Pharmacokinetic Analysis

Population parameter values were estimated using NONMEM. One, two and three compartment pharmacokinetic models were fitted to the data using subroutines from the NONMEM library (ADVAN1 TRANS2, ADVAN3 TRANS4 and ADVAN11 TRANS4 respectively). The parameters of central (V_1) and peripheral (V_2 and V_3) compartment volumes, total body clearance (CL), inter-compartmental clearance between central and peripheral 1 (Q_2) and inter-compartmental clearance between central and peripheral 2 (Q_3) were estimated for the three compartment pharmacokinetic model.

Clearance Model

$$CL_i = CL_{GRP} \cdot e^{PPV_{CL_i}}$$

$$CL_{GRP} = CL \cdot F_{WT_{CL}}$$

$$F_{WT_{CL}} = \left(\frac{WT}{WT_{STD}} \right)^{3/4}$$

PPV_{CL_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^{th} patient

Volume Model

$$V_i = V_{GRP} \cdot e^{PPV_{V_i}}$$

$$V_{GRP} = V \cdot F_{WT_V}$$

$$F_{WT_V} = \frac{WT}{WT_{STD}}$$

PPV_{V_i} was assumed to be a normally distributed random variable with mean 0

V_{GRP} is the covariate predicted group value for volume

V_i is the individual volume for the i^{th} patient.

Error Model

$$Y = F \cdot e^{ERR(1)}$$

F is the predicted propofol concentration (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.

Results and Discussion

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

Model	Description	Objective function value	No. of Structural Parameters
Base 1 comp	No covariates	-230	2
Base 2 comp	No covariates	-1092	4
Base 3 comp	No covariates	-1269	6
3 comp wt*	Weight on CL & V	-1356	6
3 comp wt age	Weight on CL & V. Age on CL	-1359	8
3 comp group	Weight on CL & V. Age on CL. Effect of group	-1362	12

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).

Table III – Final Parameter Estimates

Parameter	Estimate (95%CI)		BSV*1 (SE(CV)*2)	
CL ($L.min^{-1}.13.7kg^{-1}$)	0.185	(0.137 - 0.233)	0.658	(0.131)
V_1 ($L.13.7kg^{-1}$)	7.41	(6.52 - 8.3)	0.333	(0.060)
V_2 ($L.13.7kg^{-1}$)	54.6	(46.6 - 62.6)	0.142	(0.073)
V_3 ($L.13.7kg^{-1}$)	7.2	(5.328 - 9.072)	0.451	(0.130)
Q_2 ($L.min^{-1}.13.7kg^{-1}$)	0.614	(0.54 - 0.688)	0.348	(0.061)
Q_3 ($L.min^{-1}.13.7kg^{-1}$)	0.692	(0.558 - 0.826)	0.491	(0.097)
Proportional error	0.084	(0.123)*3		
T1/2 1 (min)	2.67			
T1/2 2 (min)	14.89			
T1/2 3 (min)	310.6			

*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

Fig. 2

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

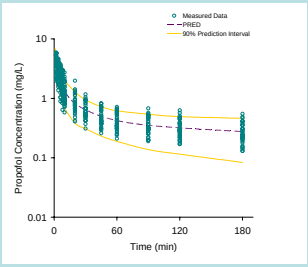
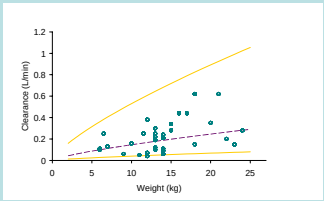


Fig. 3

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

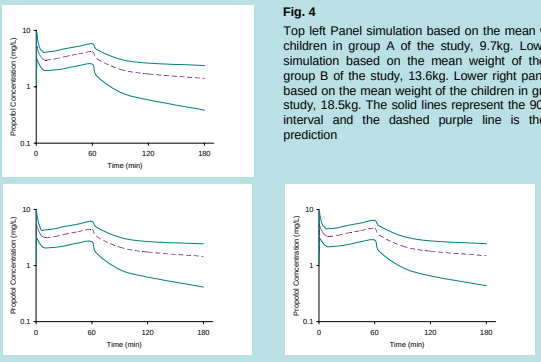


Simulation

Simulation of a 1 hour operation based on the propofol regimen described in the British National Formulary[2] 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, B and C 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.

Fig. 4

Top left Panel simulation based on the mean weight of the children in group A of the study, 9.7kg. Lower left panel simulation based on the mean weight of the children in group B of the study, 13.6kg. Lower right panel simulation based on the mean weight of the children in group C of the study, 18.5kg. The solid lines represent the 90% 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, fentanil and isoflurane. 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 treated 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.

Conclusion

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

Weight was found to be a significant covariate for the clearance and volume of distribution parameters

Age had no significant effect on clearance or volume of distribution parameters after weight had been taken into account

References

1. ShangGuan W, Lian Q, Aarons L, Matthews I, Wang ZS, Chen X, Freemantle N, Smith FG: Pharmacokinetics of a single bolus of propofol in Chinese children of different ages. Anesthesiology Accepted 2005
2. British Medical Association, Royal Pharmaceutical Association of Great Britan: British National Formulary (BNF), 49 Edition. Wallingford, Pharmaceutical Press, 2005

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