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Full Length Research paper

Validation of pharmacokinetic model of propofol in Indian population

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The pharmacokinetics of propofol has been evaluated extensively in a variety of patients groups after either bolus doses or continuous infusions. Presently there are multiple models available based on western data including China. So far, the pharmacokinetics of propofol has not been studied in the Indian population. With this background we planned to evaluate pharmacokinetics of propofol in Indian patients which will help in better management of these patients undergoing surgery using propofol infusion in total intravenous anesthesia. Venous blood samples (3 ml) for estimation of propofol concentrations were taken at different time intervals. Plasma propofol concentration was estimated by using High Performance Liquid Chromatography (HPLC) method. Maximum performance error occurred at 2 min with a median of -3.85 and it varied from -1.7 to -9.5 showing a consistent over prediction of the concentration at two minutes after the loading dose and start of infusion. Subsequently the error decreased to median of -0.9 (-0.9 to 4.6) at 10 minutes and median of -0.3 (range-0.3 to 2.8) at 30 and in 60 min -1.55(-0.28 to 1). When we compare the performance of our pharmacokinetic model of propofol in this study with other western studies, we observed less error with our pharmacokinetic model.

Key words: Propofol, pharmacokinetics, median performance error (MDPE), median absolute performance error (MDAPE).

INTRODUCTION

Propofol is an intravenous hypnotic agent which is widely used for induction and maintenance of general anesthesia. Its tremendous body uptake as well as the rapid elimination caused by huge volume of distribution and a high clearance makes propofol the best controllable intravenous anesthetic for maintenance of anesthesia at present. The pharmacokinetics of propofol has been evaluated extensively in a variety of disease states and different patients groups after either bolus doses or continuous infusions (Kay et al., 1986; Gepts et al., 1987; White and Kenny, 1990; Kirkpatrick et al., 1988; Cockshott et al., 1987). Presently there are multiple models available based on western data (Marsh et al., 1991). So far, the pharmacokinetics of propofol has not been studied in the Indian population .Previously we have studied pharmacokinetics of propofol following single bolus dose of 2 mg/kg in healthy Indian adult patients followed by serial plasma propofol concentration estimation and found Pharmacokinetic model of Propofol (Puri et al., 2012). In this present study, we planned to validate the pharmacokinetic data by targeting specific plasma propofol concentration and maintaining target plasma concentration based on our model.

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MATERIALS AND METHODS

After approval from the Institutional Ethics Committee and written informed consent, 10 ASA grade 1 20 to 40 years old Indian patients were included. All patients underwent surgeries requiring general anesthesia for less than two hours and expected blood loss less than 10% of total blood volume. Patients with previous adverse exposure to propofol and who received propofol bolus or infusion within 15 days were excluded from the study. Patients with hepatitis, HIV infection, hepatic, renal, hematological and cardio-vascular diseases were excluded from the study. No pregnant

patient and no patient with history of smoking or alcohol intake were included in the study.

Patients were premedicated with Tab Diazepam 5 mg night before as well as 2 h before induction. Before induction of anesthesia two large bore intravenous lines were secured. One in the antecubital vein and other in dorsum of the contralateral hand. The antecubital vein was used for blood sampling. Morphine 0.12 mg/kg was injected 5 min before starting propofol injection. Injection Lignocaine 2% 1 ml was injected in the iv line before injecting Propofol.

Propofol was administered as bolus dose followed by decreasing infusion rate calculated based on pharmacokinetics data of present pharmacokinetic model of propofol. The propofol infusion rate was delivered by syringe infusion pump (Pilot C Fresenius cabi) by using computer controlled. The propofol concentration was set at 3 µg/ml in 3 patients. 3.25 µg/ml in 3 patients and 3.5 µg/ml in 4 patients.

Blood sampling

Venous blood samples (3 ml) for estimation of propofol concentrations were taken at the following intervals after propofol injection and at 0 min (just before injection) and then at 2, 10, 30, and 60 min after administration of propofol bolus and infusion. Plasma propofol concentration was estimated by using HPLC method (Pavan and Buglione, 1992).

Infusion rate calculation

In the, present Propofol model, we found significant correlation in between volume of central compartment and weight of the patients and based on the equation,

Y=147.18x+4181.9

After the body weight and target concentration had been entered into the computer, loading dose was calculated based on target concentration and volume of central compartment using formula given below

LD = Target concentration × Volume of central compartment

Immediately following bolus dose, in each patient, fixed plasma concentration of propofol (3, 3.25 and 3.5 µg/ml) were maintained till the end of the surgery using decreasing infusion rate.

$R_1 = LD \times (K_{12}\, ^{e\text{-}K21t} + K_{13}\, ^{e\text{-}K31t} + K_{10})$

R is the continuously decreasing infusion rate to match the distribution into the second and third compartment; LD is the loading dose;

K_{12} = rate constant from central to tissue compartment
K_{21} = rate constant from tissue to central compartment
K_{13} = rate constant from central to deep tissue compartment.
K_{31} = rate constant from deep tissue compartment to central compartment
K_{10} = Elimination constant

And t is the time in seconds following bolus.

Mean values of rate constant obtained from present pk model

K12=0.13 K21=0.10 K13=0.05 K31=0.01 K10=0.08

Decreasing infusion rate was calculated using equation 'A' every 10 s and rate of infusion changed every 10 s by computer.

Validation of Model

Validation of model was assessed by measuring the plasma concentration at specific time intervals (2, 10, 30 and 60 min) calculating median performance error (MDPE), median absolute performance error (MDAPE), wobble, divergence (time related trends) using methods described by Varvel et al. (1991).

The predicted and measured values of propofol concentration were compared and various variables were derived as below.

Offset is the difference between predicted value and the measured value and it was calculated at each time point where measured concentrations were available that is, 2, 10, 30, and 60 min.

Offset = Measured concentration - Predicted concentration

The performance error was calculated by the formula

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

Median Performance error (MDPE)

The percentage median performance error (MDPE) which reflects the bias in the ith subject is a signed value and represents the direction (over or underprediction) of the performance error.

MDPEi= median {PEij' j= 1,…, Ni}

It is used to measure the systematic tendency of the system to underestimate or overestimate the measured concentration of blood propofol, that is, if bias has a positive value; it indicates that measured value is on an average greater than the system prediction and vice versa.

Median absolute performance error (MDAPE)

The percentage median absolute performance error (MDAPE) indicates the measure of inaccuracy in the ith subject.

MDAPEi = median {|PE| i j' j= 1,….,Ni}

Where Ni is the number of |PE| values obtained for the ith subject.

Wobble

Wobble is another index of the time related changes in performance and measures the intrasubject variability in performance errors. In the ith subject the percentage wobble is calculated as follows:

Wobble=median {|PEij –MDPEi|),j=1,….,Ni}

RESULTS

The mean age of patients in this study was 28.4 ± 6.8 years and mean weight was 55.1 ± 9.2 Kg and the mean height was 154 ± 5.2 cm (Table 1).

Propofol concentration measured in plasma at different time points in all the patients followed the target concentration fairly well (Table 2).

Maximum performance error occurred at 2 min with a median of -3.85 and it varied from -1.7 to -9.5 showing a consistent over prediction of the concentration at two

Table 1. Demographic data of the patients

Parameter	mean ± SD	Min.	Max.
Age (Years)	28.4± 6.8	20	40
Weight (Kg)	55.1 ± 9.2	40	67
Height (cm)	154 ± 5.2	148	165

(Data expressed as mean ± SD)

Table 2. Showing predicted and measured concentration at different time intervals in different patients.

S/ no	T.C ug/ml	Rate(ml/h) at 2 min	MC at 2 in ug/ml	Rate(ml/hr) at 10 min	MC at 10 m in ug/ml	Rate(ml/h) at 30min	MC at 30 m in ug/ml	Rate(ml/h) at 60 min	MC at 60 m in ug/ml
1	3	42.6	2.89	31.3	2.97	22.3	3.09	19.5	3.03
2	3	50.1	2.88	36.8	2.85	26.3	3.04	22.9	2.95
3	3	56.3	2.89	41.9	3.14	29.5	3.01	25.8	2.99
4	3.25	48.2	3.02	35.4	3.22	25.3	3.18	22	3.2
5	3.25	58.3	3.09	42.9	3.17	30.6	3.22	27.2	3.15
6	3.25	60.4	2.94	44.4	3.11	31.6	3.22	28.2	3.02
7	3.5	69.4	3.37	51	3.35	36.4	3.46	31.7	3.52
8	3.5	67.9	3.3	49.9	3.52	35.6	3.4	31.1	3.42
9	3.5	54.1	3.41	39.8	3.54	28.4	3.6	24.7	3.49
10	3.5	60.7	3.29	44.6	3.44	31.8	3.51	27.7	3.53

TC--target concn, MC--Measured concn, Concentration in µg/ml.

Table 3. The performance error showing at various time points during the study in each patient.

S.No.	Name	Sex	Age (Yrs)	Weight (KG)	Height (cm)	Surgery	TC (ug/ml)	LD (ml)	Rate (ml/h) at 2 min	MC at 2 in ug/ml	Rate (ml/h) at 10min	MC at 10 m in ug/ml	Rate (ml/h) at 30 min	MC at 30 m in ug/ml	Rate (ml/h) at 60 min	MC at 60 m in ug/ml
1	PK	F	22	40	150	Tympanoplasty	3	3	42.6	2.89	31.3	2.97	22.3	3.09	19.5	3.03
2	Suj	M	26	52	160	Cleft rhinoplasty	3	3.5	50.1	2.88	36.8	2.85	26.3	3.04	22.9	2.95
3	SR	F	39	62	148	Hysterolap	3	3.9	56.3	2.89	41.9	3.14	29.5	3.01	25.8	2.99
4	Su	F	32	43	155	Hysterolap	3.25	3.4	48.2	3.02	35.4	3.22	25.3	3.18	22	3.2
5	San	M	24	58	165	MF amputation	3.25	4.1	58.3	3.09	42.9	3.17	30.6	3.22	27.2	3.15
6	Raj	F	28	61	155	Cystectomy	3.25	4.2	60.4	2.94	44.4	3.11	31.6	3.22	28.2	3.02
7	Bim	F	30	67	154	Hysterolap	3.5	4.9	69.4	3.37	51	3.35	36.4	3.46	31.7	3.52
8	Sat	M	20	65	155	NHU R Leg	3.5	4.8	67.9	3.3	49.9	3.52	35.6	3.4	31.1	3.42
9	San	F	23	48	148	PBC neck	3.5	3.8	54.1	3.41	39.8	3.54	28.4	3.6	24.7	3.49
10	Sha	F	40	55	155	Salphingophrectomy	3.5	4.2	60.7	3.29	44.6	3.44	31.8	3.51	27.7	3.53

Table 4. Analysis of MDPE, MDAPE, WOBBLE for 10 patients

S.no.	Patients	MEAN PE	MEAN OFFSET	MDPE*	MDAPE**	WOBBLE
1	PK	-0.16	-0.005	0	2	2
2	Suj	-2.3	-0.07	-2.8	2.8	1.6
3	SR	-2.9	-0.095	-1.8	1.8	0.61
4	Su	-2.8	-0.092	-2.7	2.7	1.87
5	San	-5.4	-0.177	-5.6	5.6	2.6
6	Raj	-2.1	-0.075	-2.4	2.4	1.5
7	Bim	-2.5	-0.09	-2.5	2.5	1.74
8	Sat	0.28	0.01	0.42	1.8	1.57
9	San	-1.6	-0.05	-0.7	1.28	1.28
10	Sha	0.25	0.0075	0	2	2
	MEAN	-1.923±1.7	-0.063±0.05	-1.8±1.8	2.4±1.18	1.67±0.5
		MEDIAN	-0.0725 (-0.005~ -0.17)[#]	-2.1(0~5.6)[#]	2.2(1.8~5.6)[#]	1.67(0.61~2.6)[#]

(MDPE)* Median Performance error. (MDAPE)** Median absolute performance error. [#]Data are expressed as medians (range)

Table 5. Comparison of performance errors of present study with Western data.

Comparison of performance of our study with western data				
			PERCENTILES	
VARIABLE	GROUP	MEDIAN	10%	90%
MDPE %	**PRESENT STUDY**	**-2.1**	**-3.08**	**0.042**
	Marsh et al. (1991)	-7	-42.6	42.7
	Dyck et al. (1991)	36.4	14.3	76.5
	Tackley et al. (1989)	-4.6	-35.6	24.6
	Hung et al. (2003)	14.9		
MDAPE %	**PRESENT STUDY**	**2.488**	**1.748**	**3.08**
	Marsh et al. (1991)	18.2	8.3	43.1
	Dyck et al. (1991)	39.3	15.4	76.5
	Tackley et al. (1989)	20.6	8.3	43.1
	Hung et al. (2003)	23.3		
DIVERGENCE %	**PRESENT STUDY**	**0.2876**	**0.019**	**0.701**
	Marsh et al. (1991)	6.5	-15.1	21.9
	Dyck et al. (1991)	14.6	-61.1	42.2
	Tackley et al. (1989)	6.9	-8.4	28.9
	Hung et al. (2003)	-1.9		
WOBBLE %	**PRESENT STUDY**	**1.67**	**1.2**	**2.06**
	Marsh et al. (1991)	10	4.5	29.6
	Dyck et al. (1991)	12	7.7	21.9
	Tackley et al. (1989)	14	7.5	21.6
	Hung et al. (2003)	18.9		

minutes after the loading dose and start of infusion (Table 3 and Figure 1). Subsequently the error decreased to median of -0.9 (-0.9 to 4.6) at 10 min and median of -0.3 (range-0.3 to 2.8) at 30 and in 60 min -1.55(-0.28 to 1).

Table 4 shows the analysis of MDPE, MDAPE, WOBBLE for 10 patients. The Median prediction error (MDPE%) was found to be -2.1. The Median absolute performance error (MDAPE%) was 2.2. The wobble calculated was 1.67.

Table 5 shows the comparison of performance errors of present study with Western data. In comparison to earlier studies of Marsh et al. (1991), Dyck et al. (1991), Tackley et al. (1989) and Hung et al. (2003) evaluating various pk models of propofol (Table 5) validation of present model

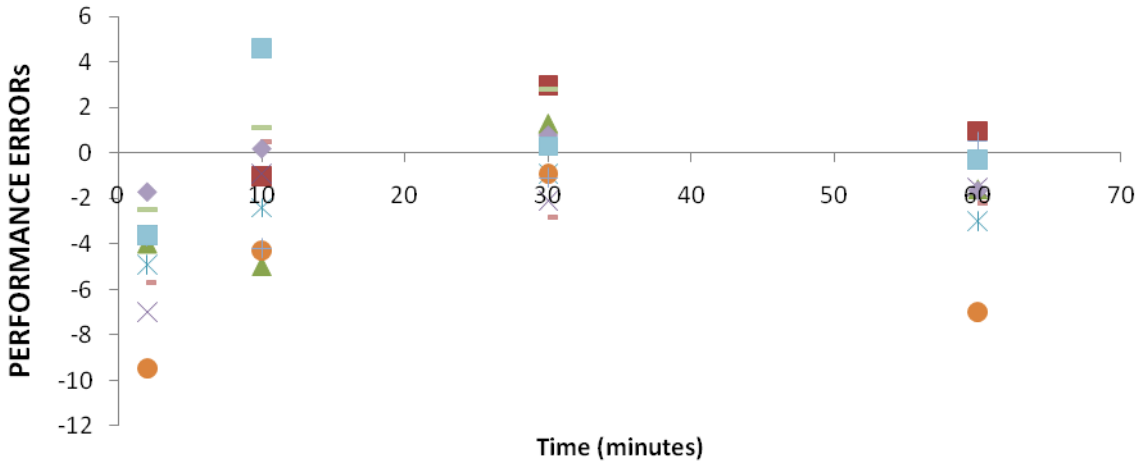

Figure 1. Showing performance error for measured concentration at various time stages.

showed better performance. The evaluation of Marsh model had to some extent comparable MDPE of -7% and MDAPE of 18.2%. Other studies like Dyck et al. (1991) showed much higher MDPE (36.45%) and MDAPE (39.3%). Similarly Tackley et al. (1989) showed MDPE % of -4.6% and MDAPE of 20.6. Hung et al. (2003) model showed 14.9% MDPE and MDAPE of 23.3% as compared to MDPE -2.1% and MDAPE 2.488% in our study**.** In our model the Median prediction error (MDPE%) was found to be -2.1 and percentiles showed that 10% values were lower than -3.08 and 90% values were lower than -0.042. The Median absolute performance error (MDAPE %) observed was 2.488 and percentiles showed that 10% values were lower than 1.748 and 90% values were lower than 3.08. The wobble calculated was 1.67 and percentiles showed that 10% values were lower than 1.2 and 90% values were lower than 2.06. When performance error of our model was evaluated with western model (Marsh et al., 1991; Dyck et al., 1991; Tackley et al., 1989; Hung et al., 2003), percentile calculation showed 10 and 90 percentile values in our study and was lower than those of western models. Thus our model showed less error compared to western models.

DISCUSSION

When we compare the performance of our pharmacokinetic model of propofol in this study with other western studies, we observed less error with our pharmacokinetic model. Though we did not evaluate other western model in our population but we compared the performance of our model obtained in present study with the performance of other models evaluated by Coetzee et al. (1995) in their respective studies. As obvious from the Table 4 we observed less error with our pharmacokinetic model. It has been suggested that the performance of a TCI system is clinically acceptable if the bias (MDPE) is no greater than 10 to 20% (Glass et al., 1990). Performance bias may be minimized by using pharmacokinetic model derived from local population and including co-variates such as, weight etc to improve the performance of such model, that is, adjusting the pharmacokinetic model to individual patient optimize the precision of TCI. The precision (MDAPE) in Marsh model was 18.3% while in our study was 2.4%. Another reason for better performance in present study may be that we kept stable propofol concentration in each patient. Variation of plasma concentration with in patients during the study may have produce different performance results. Thus in our pharmacokinetic model derived from the pharmacokinetic data from Indian population is more acceptable as the performance error calculated were less compared to the western models.

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