

# Pharmacokinetics Of Thiopental In Patients With Cardiovascular Disease

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## Abstract

Background: Cardiac output has been previously reported as a possible predictor of thiopental dose requirements. This would in turn affect the ability of a standard pharmacokinetic model (derived using data from well subjects) to predict the effect compartment concentration ( $C_e$ ) of thiopental in patients with cardiovascular (CVS) disease.

Methods: Eighty patients were given thiopental for induction of anaesthesia. Forty patients had evidence of CVS disease, while another 40 patients without CVS disease formed the control group. In each group, 20 patients received a single bolus and 20 patients received multiple small boluses. Computer simulation was then used to derive the  $C_e$ .

Results:  $C_e$  in patients with CVS disease will be under-estimated if a pharmacokinetic model derived from generally well patients is used. A new model derived to describe patients with CVS disease revealed that both the processes of drug distribution and elimination are slower in this group of patients. However, the effect compartment equilibrium half-time was also lower.

Conclusions: Pharmacokinetics of thiopental is affected by cardiovascular disease. After premedication, mean  $C_e$  at loss of the eyelash reflex for patients with or without CVS disease is  $8.51 \mu\text{g ml}^{-1}$ .

## INTRODUCTION

Anaesthetists deal with a large variety of patients, some of whom may have major physiological derangements. However, most dosing regimens have been developed based on the pharmacokinetics of the drug in healthy volunteers or in patients who are generally well. When giving thiopental to ill patients, it is considered advisable to inject the drug slowly to avoid an over-shoot of the plasma concentration, which in turn may lead to the undesirable depression of other systems.

After a bolus dose, there is a lag between the time a particular plasma concentration is reached, and the manifestation of the corresponding effect at the same concentration at steady state. Slow injection decreases this time lag, leading to a lower induction dose<sub>1</sub>. In patients without systemic diseases, the hysteresis-free effect compartment concentration at induction of anaesthesia is unaffected by the method of injection<sub>2</sub>.

The use of pharmacokinetic parameter values derived from

generally well patients in patients with cardiovascular (CVS) disease has not been fully investigated. Body weight, age and cardiac output have been previously reported as possible predictors of thiopental dose requirements<sub>3,4</sub>. The presence of CVS disease is likely to have an effect on the cardiac output, which could affect thiopental pharmacokinetics.

The aim of this study is to determine whether the predicted effect compartment concentration ( $C_e$ ) of thiopental at loss of the eyelash reflex, is the same in patients with or without CVS disease when a single parameter set is used for both groups of patients. Absence of a difference in  $C_e$  would suggest that the pharmacokinetics and pharmacodynamics in both these groups of patients are the same. A secondary aim of the study is to adapt the parameter set for use in patients with CVS disease.

## MATERIALS AND METHODS

The study was approved by the local clinical research ethics committee. Eighty patients, American Society of Anesthesiologists (ASA) physical class 1 or 2 scheduled for

elective surgical operations, gave informed consent for the study. Forty patients had evidence of CVS disease. This included patients with a history of hypertension or ischaemic heart disease, symptoms or physical signs suggestive of CVS disease, or evidence on ECG examination. Another 40 patients without evidence of CVS disease formed the control group. Patients with clinical or laboratory evidence of cardiac failure were excluded from the study.

Patients were randomized to receive thiopental either as a single bolus or as a series of small boluses for induction of anaesthesia. This resulted in a total of 4 groups:

Group 1: Patients with CVS disease who were given a single bolus

Group 2: Patients with CVS disease who were given multiple boluses

Group 3: Patients without CVS disease who were given a single bolus

Group 4: Patients without CVS disease who were given multiple boluses

All patients also received oral midazolam 3.75 mg 1 to 2 hours before induction of anaesthesia. On arrival in the operation theatre, an intravenous cannula was inserted into a forearm vein for infusion of drugs and fluid. A bolus dose of fentanyl 100 g was given 1 minute pre-induction.

Patients in groups 1 and 3 received a single 3 to 3.5 mg kg<sup>-1</sup> bolus dose injected over 10 seconds. Patients in groups 2 and 4 were given 50 mg bolus doses of thiopental every 15 seconds until loss of the eyelash reflex was demonstrated. The eyelash reflex was tested every 2.5 seconds, and the time at which the reflex was lost was recorded. After induction of anaesthesia was successfully achieved, patients were maintained using a standard anaesthetic technique.

The central compartment concentration was initially predicted using the model reported by Stanski and Maitre<sup>5</sup>. Effect compartment concentration (C<sub>e</sub>) was then calculated numerically<sup>6</sup>. The methodology has been previously described<sup>2</sup>.

In order to adapt the parameter set for patients with CVS disease, we used the Microsoft Excel Solver to minimize the difference between the mean C<sub>e</sub> of patients with CVS disease and patients without CVS disease. We denoted the model derived as the 'cardiac model'. The volume of distribution at steady state (V<sub>ss</sub>) was kept at 2.73 l kg<sup>-1</sup>.

We then repeated the process in a two stages instead of

pooling all the data together. To do this, each group was subdivided equally into 4 sub-groups and labelled 1a, 1b, 1c, 1d ... up to 4d. Four corresponding sub-groups were then combined, e.g. sub-groups 1a, 2a 3a and 4a were combined into Combination A. In this fashion, 4 combinations: A, B, C and D were obtained. Pharmacokinetic modelling was then carried out using the technique described above on each of the combinations. The derived parameter values from each combination were then prospectively tested on patients from the other sub-groups.

Differences between groups were tested using ANOVA, Student's t-test or Chi squared analysis as appropriate. Bonferroni and LSD (least significant difference) tests were used for post-hoc comparison. A value of P < 0.05 was considered significant.

## RESULTS

Demographic data is shown in Table 1.

### Figure 1

Table 1: Patient data (mean (SD)) and predicted effect compartment concentration (mean (range)). Age and weight were significantly different between groups (see text). Using the model described by Stanski and Maitre, the effect compartment concentration was significantly different between patients with and without CVS disease.

	Patients with CVS diseases		Patients without CVS diseases	
	Group 1 (single bolus)	Group 2 (multiple boluses)	Group 3 (single bolus)	Group 4 (multiple boluses)
N	20	20	20	20
Age (yr)	53.9 (9.7)	51.4 (9.3)	41.9 (11.2)	40.0 (10.7)
Weight (kg)	65.3 (8.8)	66.7 (9.0)	62.6 (7.2)	57.9 (9.7)
Gender (M / F)	9 / 11	13 / 7	7 / 13	11 / 9
Effect Compartment Conc. (µg ml <sup>-1</sup> )				
Original model (Stanski and Maitre <sup>5</sup> )	7.5 (4.9 – 9.9)	6.9 (3.7 – 11.6)	8.5 (5.6 – 12.3)	8.5 (5.7 – 15.6)
Cardiac model	8.9 (5.8 – 11.7)	8.2 (4.3 – 13.6)	-	-

Mean age was significantly different between groups (F = 9.00, P < 0.01). This difference was caused by a difference between group 1 and group 3. Mean weight was also significantly different between groups (F = 3.91, P = 0.012).

This was caused by a difference between patients with and without CVS disease. Gender distribution was not significant different between groups ( $\chi^2 = 4.00$ ,  $P = 0.26$ ). Cardiac medications taken by the patients are listed in Table 2.

Using Stanski's model, the mean  $C_e$  was significantly different between groups ( $F = 3.48$ ,  $P = 0.02$ ) (Table 1). The difference was caused by a difference between group 2 and group 3 or 4. The new model derived to reflect pharmacokinetics of thiopental in patients with CVS disease is shown in Table 3.

**Figure 2**

Table 2: Cardiovascular medication taken by patients

	Group 1	Group 2
	Single bolus	Multiple boluses
$\beta$ -blockers	8	5
Calcium channel blockers	4	8
Other medication	1	3
No medication	7	4

**Figure 3**

Table 3: Pharmacokinetic data sets for patients with or without cardiovascular diseases. The 'cardiac model' was derived using a population method.

	Original model (Stanski and Maitre <sup>3</sup> )	Cardiac model (Pooled technique)
Central Compartment Volume (ml kg <sup>-1</sup> )	79.0	79.0
Clearance (ml min <sup>-1</sup> )	3.07	1.53
Inter-compartment rate constants (min <sup>-1</sup> )		
$k_{12}$ if age < 35	0.480	0.461
$k_{12}$ if age > 35	0.48-(0.00288*(age-35))	0.461-(0.00288*(age-35))
$k_{13}$	0.107	0.088
$k_{21}$	0.079	0.080
$k_{31}$	0.0039	0.0031
Effect compartment equilibrium half-life: $t_{1/2eo}$ (min)	1.17	0.98
Volume of distribution at steady state in patients < 35 years old (ml kg <sup>-1</sup> )	2734	2734

Mean (SD)  $C_e$ , derived after combining data from all groups was 8.51 (2.00) g ml<sup>-1</sup>.

The model derived using the two-stage technique was very similar to the one derived using the pooled technique. Prospective testing of the parameter sets derived by the 4 sub-group combinations revealed that there was no significant difference between the predicted  $C_e$  of patients with or without CVS disease.

**Figure 4**

Table 4: Pharmacokinetic data sets for patients with cardiovascular disease, derived using the two stage technique. Each combination consists of 20 patients, 5 from each group. Prospective testing was done on patients not used to derived the parameter set being tested. Stanski's parameter set was used for patients without cardiovascular disease. No significant difference was found between the mean for patients with and without CVS disease in of the parameter sets teated.

	$F_1$ (ml kg <sup>-1</sup> )	Clearance (ml min <sup>-1</sup> )	$k_{12}$ (min <sup>-1</sup> )	$k_{13}$ (min <sup>-1</sup> )	$k_{21}$ (min <sup>-1</sup> )	$k_{31}$ (min <sup>-1</sup> )	$t_{y_{50}}$ (min)
Combination A	79.0	1.91	0.47	0.092	0.080	0.0033	1.03
Combination B	79.0	1.15	0.46	0.083	0.081	0.0030	0.93
Combination C	79.0	1.76	0.46	0.090	0.080	0.0032	1.01
Combination D	79.0	1.39	0.46	0.086	0.081	0.0031	0.96
Average (SD)	79.0 (0.0003)	1.55 (0.34)	0.46 (0.004)	0.088 (0.004)	0.080 (0.0002)	0.0032 (0.0002)	0.98 (0.04)

	Prospective testing		
	$C_e$ (µg ml <sup>-1</sup> ) CVS disease	$C_e$ (µg ml <sup>-1</sup> ) no CVS dis	t-test
Combination A			
Combination B	8.05	8.53	P = 0.34
Combination C	8.83	8.29	P = 0.30
Combination D	8.39	8.68	P = 0.59
Average (SD)	8.74	8.53	P = 0.69

**DISCUSSION**

In this study, we found that when the same pharmacokinetic parameter set is used to predict  $C_e$  in all groups, the patients with CVS disease appear to have loss of eyelash reflex at a lower concentration. This suggests that patients with CVS disease have either a change in the way their bodies handles the drug, or that they are more sensitive to the drug. Stanski and Maitre in their paper pointed out that age affected the pharmacokinetics, rather than the pharmacodynamics of thiopental<sub>5</sub>. This formed the basis for which we derived a new pharmacokinetic parameter set which assumed the pharmacodynamics remain unchanged.

In addition, we assumed the  $V_{ss}$  would remain unchanged. The steady state distribution of the drug is likely due to the inherent property of the drug itself, depending on its relative solubility in different tissues. Although the patients with CVS disease weighed more, and can be expected to have a different body composition, the weight normalised  $V_{ss}$  is likely to be enough to adjust for this.

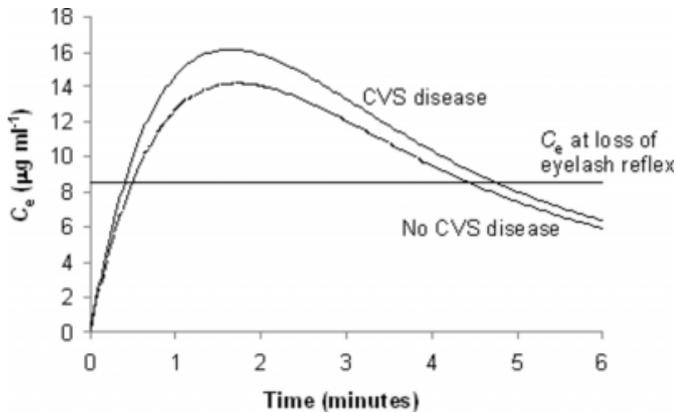
The value for the fast inter-compartment rate constant ( $k_{12}$ ) in the cardiac model is less than that reported in Stanski's original model. This means that transfer of the drug outward from the plasma is slower, and is consistent with an expected decrease in cardiac output leading to slower distribution of drug to the periphery. Elimination clearance was also found to be lower in patients with cardiac problems. This could be because of a decreased liver blood flow secondary to a lower cardiac output.

One unexpected finding was the decrease in the effect compartment equilibrium half-time. This means that when the plasma concentration is kept constant, the effect compartment would equilibrate faster with the plasma. Again, this could be an effect of a decreased cardiac output. Transit time through the brain could be slower in patients with CVS disease, allowing more time for equilibration to occur. This has the effect of allowing the brain (where the effect takes place) to have a concentration closer to that of the arterial concentration. Mathematically, this would translate to faster equilibration reflected as a lower half-time.

Figure 1 shows the effect compartment concentration – time profile after a single 3 mg kg<sup>-1</sup> bolus dose of thiopental in patients with and without CVS disease. The faster rise in patients with CVS disease is a consequence of the slower distribution to the periphery. The more prolonged effect is because of slower elimination and redistribution. What is more worrying is that  $C_e$  would reach a higher level in view of the greater plasma concentration. The same would also happen in the tissues of the cardiovascular system, leading to a more pronounced depression of the cardiovascular system. Therefore, the call to exercise extra caution when inducing anaesthesia with thiopental in such patients is well justified.

**Figure 5**

Figure 1: Effect compartment concentration-time profile in patients with or without cardiovascular disease. Patients with CVS disease have a faster rise and longer recovery. at loss of the eyelash reflex is 8.5 g ml.



The anaesthetic technique in this study included the use of midazolam as premedication, and intravenous fentanyl pre-induction. The use of midazolam premedication has been reported to decrease the induction dose of thiopental, thus decreasing the effect compartment concentration required for induction anaesthesia<sup>7</sup>. In addition, older patients are more sensitive to midazolam and fentanyl<sup>8,9</sup>. While all this would have added variability to the results, it was not appropriate to subject patients with CVS disease to pre-operative anxiety, as well as not obtunding the haemodynamic effects of endotracheal intubation.

It would have been appropriate to attempt deriving the predicted effect compartment concentration when using a continuous infusion as well. However, during the infusion, patients may experience a phase of restlessness before loss of consciousness occurs. We felt that this might cause an increase in heart rate and / or blood pressure, which would not be desirable in patients with cardiovascular disease.

In conclusion, pharmacokinetic parameter derived from generally well patients will under-predict the effect compartment concentration in patients with mild

cardiovascular disease. This is likely because of a change in pharmacokinetics in these patients. Both the processes of distribution and elimination are slower, leading a faster onset and delayed recovery. We found the effect compartment concentration at loss of the eyelash reflex for patients with cardiovascular disease to be 8.51 g ml<sup>-1</sup>.

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