Interaction between propofol and thiopental: Isobolographic analysis using dose, central compartment and effect compartment concentrations

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Citation

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Abstract

Background: Giving a benzodiazepine or opioid with an intravenous anaesthetic agent generally result in synergism. However, few studies so far have detailed the relationship when two intravenous anaesthetics are given simultaneously. The aim of this study is to investigate the interaction between propofol and thiopental when given in fixed and variable dose ratios.

Methods: Ninety patients were given propofol and / or thiopental for induction of anaesthesia. Twenty patients received an infusion of either drug while 30 patients received an infusion of an admixture of both drugs. Another 40 patients received a bolus of one drug followed by an infusion of the other. Isobolographic analysis was used to determine the interaction between the two drugs.

Results: Both fixed and variable drug dose ratios resulted in an additive interaction between propofol and thiopental. The average dose of propofol at loss of the eyelash reflex was 1.14 mg kg-1. The corresponding average thiopental dose of 2.49 mg kg-1.

Conclusions: Propofol and thiopental interact in an additive fashion when given at induction of anaesthesia.

INTRODUCTION

Planned simultaneous administration of multiple drugs exploits the beneficial effects of drug interactions. A synergistic interaction should bring about a decrease in adverse effects while maintaining the desired pharmacological effects.

Modern day anaesthetic practice attempts to apply this principle to the induction and maintenance of anaesthesia. However, the two commonly used intravenous anaesthetic agents, propofol and thiopental, act via the same mechanism and are expected to interact additively.

Vinik and colleagues reported that propofol and thiopental given as separate bolus injections resulted in an additive interaction [1]. Jones and colleagues found the same when giving an admixture of the two drugs after a dose of fentanyl [2]. Both the above studies used an isobolographic approach, and the doses of propofol and thiopental were given in predetermined ratios.

In this study, propofol and thiopental were given simultaneously during co-induction of anaesthesia in patients without preoperative sedatives or narcotics. The aim of the study is to confirm the additive interaction between propofol and thiopental under different dosing regimens. Similar to previous studies, the first part of this study involved giving propofol and thiopental in fixed ratios. In the second part, the dose ratio of the two drugs was allowed to vary.

MATERIALS AND METHODS

The study was approved by the local clinical research ethics committee. Ninety patients, American Society of Anesthesiologists physical class 1 or 2, scheduled for elective surgical operations gave informed consent for the study. Patients with a body weight above 85 kg, and patients with evidence of cardiovascular disease or a history of sensitivity to propofol or thiopental, were excluded. Patients were not given any premedication or opioids pre-operative.

In the first part of the study, 50 patients were randomized to one of five groups and were given a specific drug or drug combination for induction of anaesthesia. Drug mixtures were prepared within 30 minutes of the time of induction.

Group 1a: Propofol 10 mg ml $^{-1}$ Group 1b: Propofol 7.5 mg ml $^{-1}$ plus thiopental 6.25 mg ml $^{-1}$ Group 1c: Propofol 5 mg ml $^{-1}$ plus thiopental 12.5 mg ml $^{-1}$ Group 1d: Propofol 2.5 mg ml $^{-1}$ plus thiopental 18.75 mg ml $^{-1}$ Group 1e: Thiopental 25 mg ml $^{-1}$

In the second part of the study, patients were randomized to one of two groups. Within each group, patients were randomized to receive one of three bolus doses of a study drug. Each patient was given this bolus dose over 1 to 2 seconds, followed immediately by an infusion of the second drug.

Group 2a: Bolus dose of thiopental (50, 75 or 100 mg), followed by an infusion of propofol (10 mg ml $^{-1}$). Group 2b: Bolus dose of propofol (20, 30 or 40 mg), followed by an infusion of thiopental (25 mg ml $^{-1}$).

In all groups, the study drug or drug combination was infused at a rate of 150 ml min $^{-1}$, 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.

DATA ANALYSIS

To investigate the interaction of the two drugs, the mean dose for each group was plotted on an isobologram. The distance of the mean dose of each group from the line of addition on the isobologram was then calculated. This distance was tested against a value of zero using the paired Student's t-test. Linear regression was then carried out and the x- and y- intercepts were regarded as the average dose required for loss of the eyelash reflex.

For each patient, the predicted central compartment and effect compartment concentrations for propofol and thiopental at the recorded time point were calculated using previously reported parameter sets [3,4,5] . The methodology for calculating the effect compartment concentration has been previously described [4] . Similar isobolographic analyses were then carried out using central compartment and effect compartment concentrations in place of dose.

SPSS for Windows Release 10.0 (SPSS Inc., Chicago, ILL) was used to perform the statistical analysis. Differences between means were tested using Student's t-test or Analysis of Variance (ANOVA) as appropriate. Chi-square test was used for categoral data. A value of $p < 0.05$ was considered significant.

RESULTS

A total of 27 male and 63 female patients were admitted into the study. The mean age, mean weight and gender distribution are given in Table 1. There were no significant differences in demographic data between groups. Table 2 shows the dose and predicted drug concentration at loss of the eyelash reflex.

Figure 1

Table 1: Patient data (mean (SD)). Prop:Thio ratio refers to the ratio of propofol (10 mg ml) to thiopental (25 mg ml) in terms of volume. B = bolus ; I = infusion.

	Infusion of both propofol and thiopental					Bolus of one drug ; infusion of a second	
	Gp 1a	Gp 1b	Gp 1c	Gp 1d	Gp 1e	Gp 2a	Gp 2b
Prop:Thio ratio	4 : 0	3 : 1	2 : 2	1 : 3	0 : 4	B: Thio I: Prop	B: Prop I: Thio
n	10	10	10	10	10	20	20
Age (yr)	36.3 (13.9)	38.3 (16.5)	37.2 (14.0)	35.6 (10.9)	38.2 (12.5)	36.0 (12.0)	32.0 (9.7)
Weight (kg)	60.7 (11.5)	58.0 (14.5)	56.2 (7.2)	62.1 (9.7)	62.2 (9.5)	63.5 (11.3)	59.0 (9.9)
Gender (M / F)	2 / 8	2 / 8	3 / 7	3 / 7	4 / 6	5 / 15	8 / 12

Figure 2

Table 2: Dose and predicted drug concentration at loss of the eyelash reflex (mean (SD)).

	Infusion of both propofol and thiopental					Bolus of one drug ; infusion of a second	
	Gp 1a	Gp 1b	Gp 1c	Gp 1d	Gp 1e	Gp 2a	Gp 2b
Prop:Thio ratio	4 : 0	3 : 1	2 : 2	1 : 3	0 : 4	B: Thio I: Prop	B: Prop I: Thio
n	10	10	10	10	10	20	20
Induction dose (mg kg^{-1})							
Propofol	1.13 (0.33)	0.79 (0.19)	0.53 (0.17)	0.26 (0.04)	-	0.65 (0.34)	0.51 (0.13)
Thiopental	-	0.66 (0.16)	1.33 (0.43)	1.92 (0.30)	2.46 (0.57)	1.16 (0.26)	1.46 (0.47)
Predicted central compartment concentration (μg ml^{-1})							
Propofol	3.53 (0.94)	2.55 (0.53)	1.70 (0.45)	0.81 (0.08)	-	2.20 (0.93)	1.58 (0.53)
Thiopental	-	4.57 (0.94)	8.38 (2.29)	12.7 (1.16)	16.9 (3.18)	5.90 (2.83)	12.4 (3.19)
Predicted effect comp. concentration (μg ml^{-1})							
Propofol	2.28 (0.70)	1.49 (0.43)	1.00 (0.41)	0.49 (0.10)	-	1.12 (0.86)	1.19 (0.28)
Thiopental	-	2.40 (0.66)	4.48 (1.92)	7.06 (1.36)	9.10 (2.27)	5.20 (1.14)	4.38 (1.91)

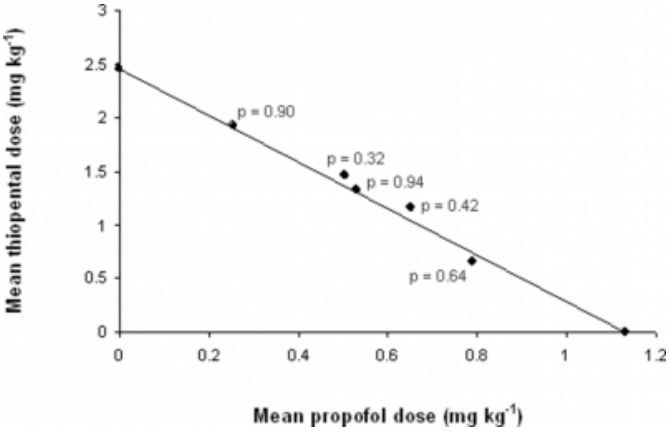
Figure 1 shows the relationship between the mean doses of propofol and thiopental at loss of the eyelash reflex. There was no significant difference between the mean dose for each group and its corresponding predicted dose on the line of addition. Using linear regression, the average dose at loss of the eyelash reflex for propofol and thiopental were 1.14 mg kg $^{-1}$ and 2.49 mg kg $^{-1}$ respectively.

Figure 2 shows the distribution of the mean predicted central compartment concentrations. In Group 2b, the mean concentrations of propofol and thiopental were significantly higher than those expected if the line of addition was followed ($p<0.001$).

Figure 3 shows the distribution of mean effect compartment concentrations. All predicted concentrations were not significantly different from the line of addition.

Figure 3

Figure 1: Relationship between mean doses of propofol and thiopental at loss of the eyelash reflex. Each circle represent the mean dose derived from a group of patients.



The line joining the mean doses of propofol and thiopental when given alone, is the line of addition. Isobolographic analysis reveals an additive interaction.

Figure 4

Figure 2: Propofol vs. thiopental predicted central compartment concentration at loss of the eyelash reflex. Each circle represents a group of patients. Isobologrphic analysis suggest that in Group 2b (open circle), the relationship is antagonistic.

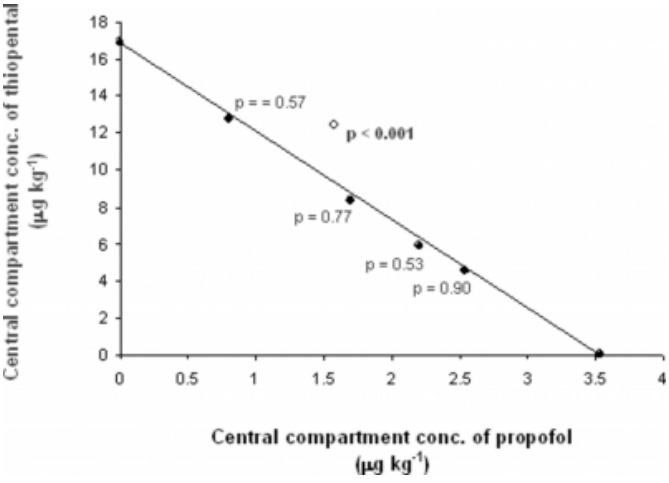
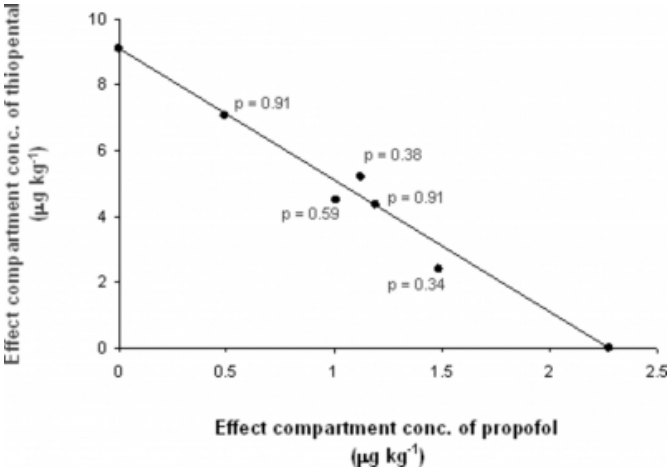


Figure 5

Figure 3: Propofol vs. thiopental effect compartment concentration at loss of the eyelash reflex. Each circle represents a group of patients. There is no significant difference between any circle and its corresponding point on the line of addition.



DISCUSSION

In clinical practice, it is not unusual for several drugs to be given together in order to obtain a specific pharmacological effect. However, combining drugs with similar effects may result in synergistic, additive or antagonistic interactions. This was reported in a recent study on anticonvulsants [6].

The same has been shown with pharmacological agents used to produce hypnosis. Midazolam has been reported to act synergistically with propofol and thiopental [7,8]. In contrast, propofol and sevoflurane interact in a simple additive manner to produce loss of consciousness [9]. The interaction between nitrous oxide and propofol for the suppression of blood pressure elevation also appears to be additive [10].

This study confirmed earlier reports that the hypnotic effect of propofol and thiopental when given together is additive [1,2,10]. However, the design of our study is quite different from the earlier studies.

In the study by Vinik and colleagues, the doses of propofol and thiopental which were given to the patients were fixed, and the end-point was reached in some patients but not in others [1]. In our study, the doses of propofol and thiopental were allowed to vary according to the patients' requirement. All of our patients reached the pharmacodynamic end-point. Despite the differences in methodology, the average dose of propofol and thiopental obtained in Vinik's study were very close to the values we obtained.

Unlike the study by Jones and colleagues, we did not give opioids to any of our patients before induction of anaesthesia [2]. Opioids have been reported to act synergistically with propofol and thiopental [12,13]. When all three drugs are given together, the extent to which fentanyl affects the propofol dose may not be the same as the extent to which it affects the thiopental dose. The quantity of effect from three-drug combinations is difficult to predict. Short and colleagues reported that the effect of a midazolam-propofol-alfentanil combination was less than expected although it was still synergistic [14]. Our study was designed to avoid such a situation.

Most isobolographic studies use fixed drug dose ratio combinations. Whether the method can be adapted to variable drug dose ratios has not been well documented. This study illustrates that it is possible to use isobolographic analysis when drugs are given in variable dose ratios. Such a condition better resembles the actual clinical situation.

We also demonstrated that the isobolographic analysis could be applied to effect compartment concentrations. However, the same could not be applied to predicted central compartment concentrations. In the group of patients who received a bolus of propofol followed by an infusion of thiopental, the relationship appeared to be antagonistic. This is most likely because of a delay in the equilibration between the central and effect compartments. This results in the predicted central compartment concentration being higher than expected, giving an impression that the relationship is antagonistic. Our study therefore supports the practice of using effect compartment concentrations, rather than central compartment concentrations, to predict effect.

The practical uses of propofol-thiopental combinations have been previously studied. Pre-treatment or co-administration of thiopental has been reported to reduce the incidence of pain on injection with propofol [10,15,16,17,18]. The propofol-thiopental admixture has also been shown to produce suitable conditions for laryngeal mask insertion [19]. Furthermore, giving such an admixture for induction of anaesthesia produced less hypotension compared to giving propofol alone [2,10,19].

One of the worries with mixing two drugs is that the undesirable effects of both drugs would contribute to the overall patient morbidity. It has been argued that adding thiopental to propofol for induction would remove some of the advantages associated with propofol [20]. However, studies

have shown that the mean discharge time in patients who were given a propofol-thiopental admixture was not different from patients who were given propofol alone or with lignocaine [21,22] . These studies also reported that the incidence of severe nausea or need for anti-emetics were not increased.

In conclusion, we studied the hypnotic effect of propofol and thiopental when given together and found the effect to be additive at the range of doses used for induction of anaesthesia.

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