Isobolographic Analysis of the Hypnotic Interaction Between Propofol and Thiopental

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ABSTRACT

Introduction: Giving two intravenous anaesthetic agents simultaneously generally results in an additive effect. The aim of this study was to investigate the interaction between propofol and thiopental when given to patients who have had sedative premedication. **Methods:** Fifty patients were admitted into the study. All patients received oral midazolam 3.75 mg and intravenous fentanyl 100 mg before induction of anaesthesia. Twenty patients received an infusion of either propofol or thiopental while 30 patients received an infusion of an admixture of both drugs. Isobolographic analysis was used to determine the interaction between the two drugs. **Results:** The interaction between propofol and thiopental was additive. The average dose at loss of the eyelash reflex for propofol and thiopental was 0.71 mg kg^{-1} and 1.54 mg kg^{-1} respectively. Premedication decreased the induction dose by 38.2%. **Conclusion:** Propofol and thiopental interact in an additive fashion when given at induction of anaesthesia.

Keywords: Anaesthetics, intravenous, isobologram, propofol, synergism, thiopental

INTRODUCTION

Modern day anaesthetic practice usually involves the simultaneous administration of multiple drugs to create a required degree of depression of the central nervous system. What is hoped for is a synergistic interaction which should bring about the desired pharmacological effects but with a lower incidence of adverse effects.

The two commonly used intravenous anaesthetic agents, propofol and thiopental, act via the same mechanism and are expected to interact additively. This had been shown by Vinik and colleagues who gave propofol and thiopental as separate bolus injections. [1] Jones and colleagues found the same when giving an admixture of the two drugs after a dose of fentanyl. [2] A recent report confirmed the additive interaction when infusing the drug combination simultaneously into unpremedicated patients. [3]. All the above studies used an isobolographic approach.

Oral benzodiazepines are frequently given to patients who are on their way to the operation theatre. This helps to reduce anxiety and make the whole experience less unpleasant. Being a central nervous system depressant, midazolam usually causes a decrease in the amount of anaesthetic agent required for induction of unconsciousness. However, the effect of benzodiapedines on the interaction between propofol and thiopental has not been fully documented.

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The aim of the study was to confirm that the interaction between propofol and thiopental is additive when administered to patients who were given benzodiazepine premedication. In addition, this study was carried out to provide further information on the decrease in the dosage of intravenous induction agents in patients who had received sedative premedication. This would help anaesthetists make adjustments to the dose of anaesthetic agents in the presence of other central nervous system depressants.

METHODS

The study was approved by the local clinical research ethics committee. Fifty patients, categorised as 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, or who had a history of hypersensitivity to propofol or thiopental, were excluded. All patients were given oral midazolam 3.75 mg as premedication when called to the operation theatres. Intravenous fentanyl 100 mg, was given 1 minute before induction of anaesthesia.

The patients were randomised to one of five groups and were given a specific drug or drug combination for induction of anaesthesia. Randomisation was done by opening a book and dividing the even page number by 5. Once the number of patients in a particular group reached 10, the group was excluded from the randomisation process.

Drug mixtures were prepared within 30 minutes before the time of induction by an assistant who was not involved in the determination of the onset of anaesthesia.

Group 1: Propofol 10 mg ml^{-1}
Group 2: Propofol 7.5 mg ml^{-1} plus thiopental 6.25 mg ml^{-1}
Group 3: Propofol 5 mg ml^{-1} plus thiopental 12.5 mg ml^{-1}
Group 4: Propofol 2.5 mg ml^{-1} plus thiopental 18.75 mg ml^{-1}
Group 5: 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.

For each patient, the dose of propofol and thiopental required was calculated by multiplying the time taken for induction with the rate of infusion, and dividing by the patient's weight.

Data Analysis

To investigate the interaction of the two drugs, the mean dose of propofol and thiopental for each group was plotted on an isobologram. The distance of the plotted points for Groups 2, 3 and 4 from their expected point on the line of addition was then calculated. This distance was tested against a value of zero using the one sample Student's *t*-test. Data from Groups 2, 3 and 4 were then pooled together and the resultant mean dose was compared with the mean dose predicted from the line of addition.

Linear regression was performed with the dose of thiopental as the dependent variable and dose of propofol as the independent variable. The regression was then repeated with the value for the gradient taken from an earlier report using a similar methodology but without the administration of any premedication or opioids preoperatively. [3] The x- and y-intercepts derived from the second linear regression were regarded as the average doses of propofol and thiopental required for loss of the eyelash reflex. The ratio between the induction dose determined in this study and the corresponding dose in unpremedicated patients was then determined.

SPSS for Windows Release 14.0 (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 categorical data. A value of $p < 0.05$ was considered significant.

RESULTS

A total of 17 male and 33 female patients were admitted into the study. The mean age, weight, dose and gender distribution are given in Table 1. There were no significant differences in age ($F = 0.65$, $p = 0.61$), weight ($F = 2.21$, $p = 0.08$) or gender distribution ($\chi^2 = 1.43$, $p = 0.84$).

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. This indicates that the interaction is additive.

Table 1. Patient data and dose at loss of the eyelash reflex (mean (SD)).

	Gp 1	Gp 2	Gp 3	Gp 4	Gp 5
Prop: Thio ratio	4 : 0	3 : 1	2 : 2	1 : 3	0 : 4
n	10	10	10	10	10
Age (yr)	40.3 (13.0)	41.3 (8.1)	39.7 (14.0)	45.3 (7.1)	46.0 (13.3)
Weight (kg)	67.0 (9.4)	65.1 (10.8)	55.2 (10.2)	60.1 (11.9)	60.1 (6.8)
Gender (M / F)	2 / 8	4 / 6	3 / 7	4 / 6	4 / 6
Induction dose ($mg.kg^{-1}$)					
Propofol	0.64 (0.08)	0.46 (0.15)	0.36 (0.12)	0.18 (0.06)	-
Thiopental	-	0.38 (0.12)	0.91 (0.30)	1.34 (0.46)	1.49 (0.27)

Note: Prop: Thio ratio refers to the ratio of propofol (10 mg ml^{-1}) to thiopental (25 mg ml^{-1}) in terms of volume.

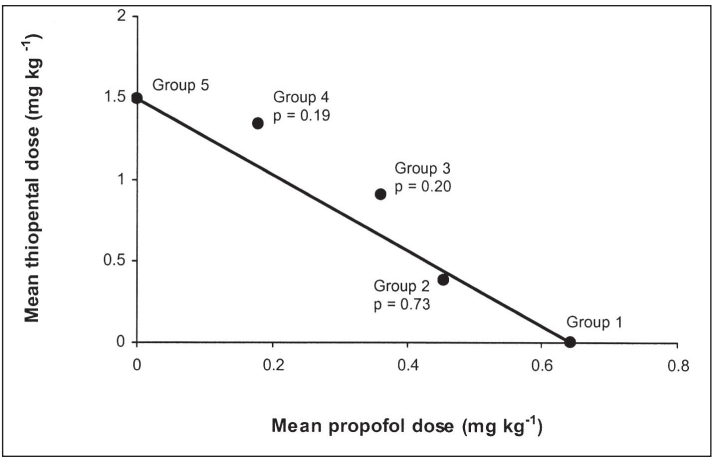

Figure 1. Relationship between mean doses of propofol and thiopental at loss of eyelash reflex. Each circle represents mean dose derived from a group of patients. Line joining mean doses of propofol ad thiopental when given alone, is the line of addition. Isobolographic analysis reveals an additive interaction.

The mean dose obtained from pooling data from Groups 2, 3 and 4 was also not significantly different from the mean predicted dose ($p = 0.13$).

Using linear regression, the gradient of the slope was found to be -2.47 (95% CI -2.93 to -2.0). The relative potency reported in the earlier study on unpremedicated patients (-2.18) fell within the derived 95% CI. Repeating the regression using the gradient of -2.18, the doses at loss of the eyelash reflex for propofol and thiopental were 0.71 mg kg^{-1} and 1.54 mg kg^{-1} respectively (Figure 2).

The dose ratio between unpremedicated and premedicated patients was 1.62. This means that the percentage decrease in drug dosage with premedication was 38.2%.

DISCUSSION

Combining drugs with similar effects may result in synergistic, additive or antagonistic interactions. Such interaction has been investigated using anticonvulsants as well as hypnotic agents. [4] Midazolam has been reported to act synergistically with propofol and thiopental.[5,6] In contrast, propofol and sevoflurane interact in a simple additive manner to produce loss of consciousness.[7] Similarly, the interaction between nitrous oxide and propofol for the suppression of blood pressure elevation appears to be additive.[8]

While previous studies have shown the hypnotic effect of propofol and thiopental to be additive, the present study differs from those previous studies in a number of ways.[1,2,9] Vinik and colleagues used fixed doses of propofol and thiopental, and the end-point was reached in some patients but not in others.[1] We allowed the doses of propofol and thiopental to vary according to the patients' requirement. As such, all of our patients reached the pharmaco-dynamic end-point.

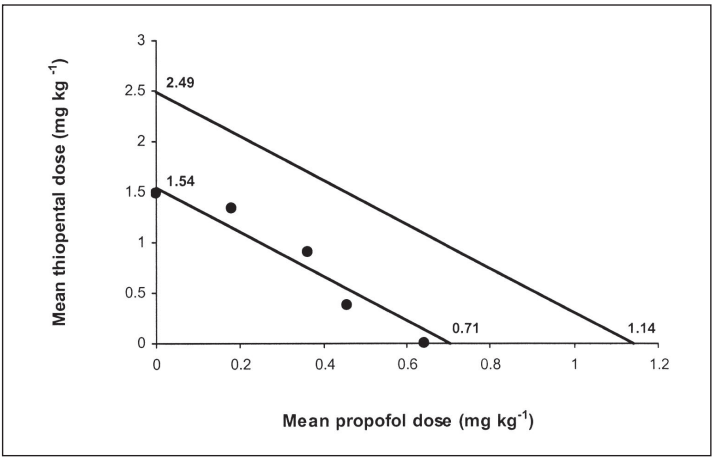

Figure 2. Relative potency of propofol and thiopental in premedicated and unpremedicated patients. Upper line joins the mean doses required in unpremedicated patients while lower line shows relationship in premedicated patients – this line was derived using linear regression with gradient equal to that of the upper line.

While Jones and colleagues did give opioids to their patients before induction of anaesthesia, we gave our patients opioids and midazolam as premedication.[2] Opioids have been reported to act synergistically with propofol and thiopental.[10,11] When all four drugs are given together, the extent to which fentanyl and midazolam affects the propofol and thiopental dose is difficult to predict.

We were pleasantly surprised when we found the interaction could still be analysed using an isobologram, and that the relationship remained additive. This fact is supported by the finding of a similar relative potency with or without midazolam premedication and intravenous fentanyl. Had the premedication affected one anaesthetic agent more than the other, the gradient of the slope would have changed. There appears to be a consistent decrease in anaesthetic drug requirement, which averaged around 38%.

The practical uses of propofol-thiopental combinations are well studied. Pre-treatment or co-administration of thiopental may reduce the incidence of pain on injection with propofol.[9,12,13] Using a propofol-thiopental admixture has also been shown to produce suitable conditions for laryngeal mask insertion. Furthermore, giving such an admixture for induction of anaesthesia produced less hypotension compared to giving propofol alone.[2,9,14]

A major concern about mixing two drugs is that the undesirable effects of both drugs would contribute to overall patient morbidity. It has been argued that adding thiopental to propofol for induction would remove some of the advantages associated with propofol.[15] 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.[16,17] These studies also reported that the incidence of severe nausea or need for anti-emetics were not increased.

CONCLUSION

In conclusion, we studied the hypnotic effect of propofol and thiopental when given together in patients premedicated with midazolam and fentanyl, and found the effect to be additive at the range of doses used for induction of anaesthesia. When giving intravenous anaesthetics to patients who have been given sedative premedication, it would be prudent to reduce the starting dose by one-third.

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