THIOPENTONE-PROPOFOL HYPNOTIC SYNERGISM IN PATIENTS

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SUMMARY
The hypnotic effects of thiopentone, propofol and their combination were studied in 120 unpremedicated ASA group I patients. The end-point for induction of anaesthesia was taken as inability to open the eyes to command 60 s after the end of injection. The dose-response curves were determined by probit analysis. Isobolographic and algebraic (fractional) analyses were used to assess quantitatively the combined hypnotic effect of thiopentone and propofol and to define the type of interaction between these two drugs. The interaction between thiopentone and propofol was found to be synergistic.

KEY WORDS
Anaesthetics, intravenous; thiopentone, propofol. Interactions (drug): thiopentone, propofol. Potency: ED₅₀

Propofol represents a new class of i.v. anaesthetic agents, which is unrelated chemically to the barbiturates, steroid or eugenol agents.

Barbiturates are thought to exert many of their effects via enhancement of gamma-aminobutyric acid (GABA)-mediated inhibition in the central nervous system [1, 2]. Components of the GABA receptor-ionophore complex include the GABA receptor, chloride ion channel, benzodiazepine binding site and barbiturate-picrotoxin-meprobamate binding site [3]. Barbiturates increase chloride ion flux through the channel, and thereby cause hyperpolarization of the postsynaptic membrane, inhibiting conductance [1—3]. In addition, there is evidence that barbiturates may interact directly with the chloride channel [4]. Propofol probably acts by modulation of GABA neurotransmission, although the exact mechanism is unknown [1].

A combination of agents with effects greater than expected from its constituents is said to show synergism. A combination with actions less effective than expected is said to show antagonism, and one no more and no less effective than expected is said to show additive effects. Synergy and antagonism imply that the constituents affect each other’s action—that is, they interact pharmacologically [5].

This study was designed to quantify the combined hypnotic effect of thiopentone and propofol and to define the type of interaction between the two drugs.

PATIENTS AND METHODS
After obtaining institutional approval and informed consent, we studied 120 ASA group I unpremedicated patients aged 20–45 yr admitted for minor surgical procedures. Patients who had taken benzodiazepines, opioid drugs or other sedative agents within 1 month of the investigation were excluded. Three groups were studied: one group received thiopentone, the two others received either propofol or a thiopentone–propofol combination. The following predetermined doses of drugs were administered to subgroups of six patients: thiopentone 2, 2.5, 3, 4, 4.5, 5, 5.5, 6 mg kg⁻¹; propofol 1, 1.2, 1.5, 1.7, 2, 2.25, 2.4 mg kg⁻¹; thiopentone and propofol, respectively, 0.86 and 0.3, 0.86 and 0.6, 0.86 and 0.8, 0.86 and 0.9, 0.86 and 1.1 mg kg⁻¹. Patients were assigned at random to the subgroups and stratified sampling was used to obtain an even sex distribution. Studies of the single-drug groups were

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THIOPENTONE–PROPOFOL SYNERGISM

Fig. 1. Thiopentone (T) and propofol (P) quantal dose–response curves. The horizontal lines at the ED$_{50}$ level indicate 95% confidence limits.

Fig. 2. ED$_{50}$ isobologram for the interaction of thiopentone and propofol assessed by loss of response to verbal command 60 s after induction of anaesthesia. ED$_{50}$ values indicate the dose that provides the effects in 50% of patients when each drug is used alone. The straight line connecting the single-drug ED$_{50}$ points is the additive line. *P < 0.05 (level of statistical significance for deviation of the combined ED$_{50}$ point from the additive line).

concluded first, so that doses for the combination could be planned.

All drugs were injected in 15 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. catheters inserted in one arm. An investigator, unaware of which drug had been injected, assessed the patient’s level of consciousness. Abolition of the ability to open the eyes on command, 60 s after the end of injection, was used as an end-point of anaesthesia.

Dose–response curves and ED$_{50}$ values were determined by fitting the number of patients unable to respond to the command at each dose to a probit model [6] using PCNONLIN [7]. Isobolographic [8, 9] and algebraic (fractional) [5] analyses were used (ED$_{50}$ level) to define the type of interaction between thiopentone and propofol. With isobolographic analysis, ED$_{50}$ values from all groups of patients were plotted in the form of an isobol. Single-drug ED$_{50}$ points were placed on the dose co-ordinates of the isobologram, and a combined ED$_{50}$ point in the dose field. A straight line joining the single-drug ED$_{50}$ points is termed the “additive line” and the deviation of the ED$_{50}$ of a combination to the left indicates synergism. The deviation of a combined ED$_{50}$ point from the additive line was measured as the length along a line running from the point in question to the additive line perpendicular to it. The se of this distance was computed by the method of propagation of error [10], and error estimates from a combined ED$_{50}$ point and single-drug ED$_{50}$ points were used. An approximate $t$ test used to test the assumption of additivity was obtained as the ratio of the measured distance to its standard error [11].

Algebraic (fractional) analysis was based on the expression of the component doses of thiopentone and propofol of the combination (Tc and Pc) as fractions of the doses that produce the same effect when given separately (Tc/Ts and Pc/Ps). The sum of fractional doses equals to 1.0 in summation, as expressed by the following equation:

$$\frac{Tc}{Ts} + \frac{Pc}{Ps} = 1.0$$

In synergism, the sum of fractional doses is less than 1.0, and in antagonism it is greater than 1.0.

RESULTS

The groups were comparable with respect to age and weight. The calculated ED$_{50}$ values for thiopentone and propofol were 1.9 mg kg$^{-1}$ (95% confidence limits, 1.3–2.7 mg kg$^{-1}$) and 1.17 mg kg$^{-1}$ (95% confidence limits, 0.9–1.4 mg kg$^{-1}$) respectively. Comparison of the thiopentone and propofol dose–response curves showed that the difference between slopes was not statistically significant (the 95% confidence limits overlapped) (fig. 1).
On the thiopentone–propofol isobologram for ED$_{50}$ doses, the combined ED$_{50}$ point deviated to the left ($P < 0.05$) from the additive line, indicating synergism (fig. 2). The fractional (algebraic) analysis of this interaction also demonstrated synergism by virtue of the smaller fractional dose needed for the same effect with combined administration (table I).

**DISCUSSION**

The ED$_{50}$ value of 1.9 mg kg$^{-1}$ for thiopentone found in this study is close to the ED$_{50}$ value for thiopentone (2.2 mg kg$^{-1}$) reported by Stella, Torri and Gastiglioni [12] in premedicated patients, and that reported by Tverskoy and colleagues [13] in unpremedicated patients (2.9 mg kg$^{-1}$). In the latter study, the response to verbal command was assessed 2 min after injection of thiopentone. Grounds, Moore and Morgan [14], using a different methodology, reported that the ED$_{50}$ for propofol was 1.6 mg kg$^{-1}$ and the potency of propofol to thiopentone was 1:1.604. These values are in agreement with our results.

We calculated the ED$_{50}$ for thiopentone and propofol at 60 s after injection because Cote and colleagues [15] demonstrated a variability in response 30 s after injection of thiopentone, while the response at 60 s was more constant.

Isobolographic and algebraic analyses used in this study demonstrated a synergistic thiopentone–propofol interaction in relation to the hypnotic effect. The combination of the two drugs gave an ED$_{50}$ which was 0.84 of the fractional dose needed for ED$_{50}$ for each drug when given alone. The synergistic interaction between thiopentone and propofol may be explained on the basis of interaction at the GABA receptor complex.

**REFERENCES**