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PROPOFOL AND MIDAZOLAM ACT SYNERGISTICALLY IN COMBINATION

T. G. SHORT AND P. T. CHUI

SUMMARY

We have studied interactions between i.v. propofol and midazolam for induction of anaesthesia in 200 unpremedicated female patients undergoing elective gynaecological surgery. Using end-points of "hypnosis" (loss of response to verbal command) and "anaesthesia" (loss of response to a 5-s transcutaneous tetanic stimulus), we determined dose–response curves for propofol and midazolam alone and in combination. For hypnosis, synergistic interaction was found ($P < 0.01$), the combination having 1.44 times the potency of the individual agents. Although midazolam failed to produce anaesthesia in the dose range used, the dose of propofol required to produce anaesthesia was reduced by 52% in the presence of midazolam ($P < 0.01$). The reduction in arterial pressure at induction was the same for the combination as for the individual agents. The cause of the synergism was not clear, but may have been interaction at CNS $GABA_A$ receptors.

KEY WORDS

Anaesthetics, intravenous: propofol. Hypnotics, benzodiazepines: midazolam. Induction. Pharmacology: drug interactions.

Several i.v. agents, including thiopentone [1, 2], fentanyl [3] and alfentanil [4, 5] have been shown to act synergistically when given in combination with midazolam at induction of anaesthesia using the end-point of hypnosis (loss of response to verbal command) to define successful induction. The use of propofol in combination with midazolam has been studied also [6], but the nature of the sedative interactions is not known.

In this study we examined the interaction between propofol and midazolam when combined for induction of anaesthesia at two end-points that correspond to hypnosis and anaesthesia.

PATIENTS AND METHODS

After approval from the Research Ethics Committee of the Chinese University Faculty of Medicine, we studied 200 adult Chinese female patients who presented for elective gynaecological surgery and gave informed consent. Criteria for entry into the study were: age 18–40 yr, ASA grade I or II, no recent ingestion of psychotropic medication and weight within 20% of ideal. All patients were unpremedicated.

In the first part of the study, dose–response relationships were established for propofol and midazolam given individually. One hundred and twenty patients were allocated randomly to 12 groups of 10, each receiving one of seven doses of propofol (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, 2.5 mg kg^{-1}) or one of five doses of midazolam (0.1, 0.125, 0.15, 0.175, 0.2 mg kg^{-1}). The midazolam doses were determined from previous work undertaken by one of the authors [1] and the propofol doses from a pilot study. All drugs were injected over 10 s into a forearm vein, followed by flush with 10 ml of physiological saline. The observer was blind to the dose given.

Patients were assessed for hypnosis and anaesthesia 2 min after propofol and 4 min after midazolam, these times being the approximate time to peak effect of each drug when given as an i.v. bolus. Hypnosis was assessed as failure to open the eyes on verbal command. In those patients who achieved hypnosis, anaesthesia was assessed as failure to respond to a standard 5-s transcutaneous tetanic stimulus (50-Hz, 80-mA, 0.25-ms pulses) over the ulnar nerve—an end-point shown to equate to MAC for volatile

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TABLE I. *Proportions of patients achieving hypnosis and anaesthesia and mean (SD) decrease in mean arterial pressure (MAP) at 2 min, after each dose of propofol, midazolam or the combination*

Drug dose (mg kg^{-1})				
Midazolam	Propofol	Proportion hypnotic	Proportion anaesthetized	Decrease in MAP (mm Hg)
0.1	0	0.2	0	14.7 (14.3)
0.125	0	0.3	0	18.0 (10.9)
0.15	0	0.5	0	12.5 (12.4)
0.175	0	0.8	0	10.9 (7.2)
0.2	0	0.8	0	10.0 (7.1)
0	0.7	0.1	0	12.7 (11.2)
0	1.0	0.3	0	11.9 (8.1)
0	1.3	0.9	0	10.9 (7.2)
0	1.6	1.0	0.3	16.7 (9.9)
0	1.9	1.0	0.3	12.0 (10.4)
0	2.2	1.0	0.7	7.3 (13.6)
0	2.5	1.0	0.9	12.5 (8.7)
0.03	0.21	0.2	0	6.8 (5.0)
0.04	0.29	0.4	0	11.8 (14.7)
0.05	0.36	0.5	0	10.4 (12.1)
0.065	0.46	0.8	0	11.6 (14.1)
0.085	0.60	1.0	0	16.8 (9.3)
0.10	0.71	1.0	0.1	20.3 (10.5)
0.13	0.92	1.0	0.4	17.0 (7.6)
0.17	1.2	1.0	0.9	15.5 (13.6)

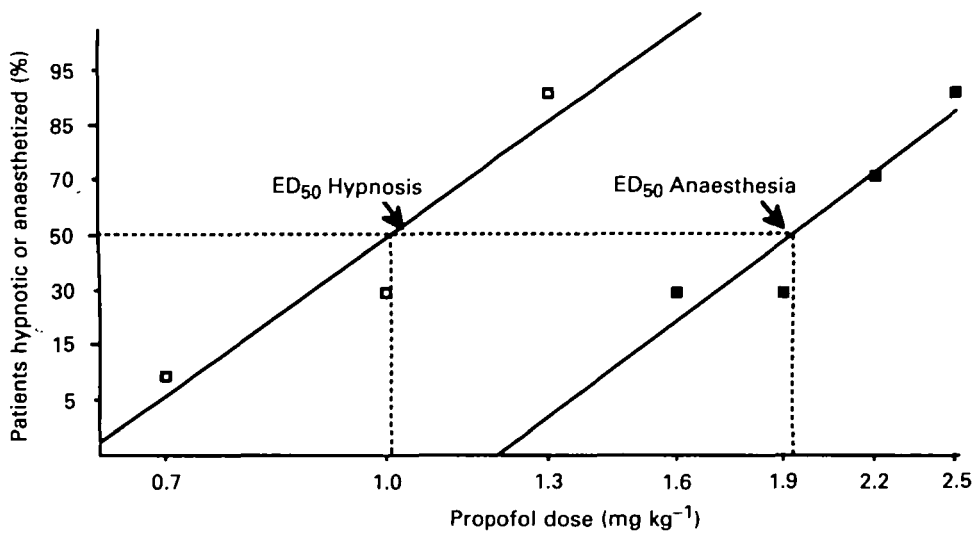

FIG. 1. Hypnotic (□) and anaesthetic (■) (log)dose–(probit)response relationships for propofol. The ED_{50} for hypnosis was 1.01 mg kg^{-1} and that for anaesthesia 1.93 mg kg^{-1}.

anaesthetics [7]. Arterial pressure was recorded at 1-min intervals during the observation period, using an automated oscillometric arterial pressure recorder (Dinamap 1846SX, Critikon).

In the second part of the study, we examined propofol and midazolam given in combination. Beginning with a combination of 50 % of the ED_{50} for hypnosis for each drug, we chose five doses smaller than this and two doses greater, whilst maintaining a constant dose ratio. The doses of propofol and midazolam, respectively, were 0.21/0.03, 0.29/0.04, 0.36/0.05, 0.46/0.065,

0.60/0.085, 0.71/0.10, 0.92/0.13 and 1.2/0.17 mg kg^{-1}. Midazolam was administered 2 min before propofol and a further 2 min was allowed before assessment, so that both drugs would be reaching peak effect at approximately the same time.

Statistical analysis was performed using analysis of variance to compare age, weight and arterial pressure measurements in patient groups. For graphical display and calculation of ED_{50} values for hypnosis and anaesthesia the log(dose)–response curves were linearized using probit transformation [8]. When the proportion of patients achieving hypnosis or anaesthesia was 0 or 1.0, the data were excluded from subsequent analysis.

Interactions using the hypnotic end-point were examined by the method of Plummer and Short [9]. It is an extension, to the case of non-parallel log(dose)–response curves, of a method described by Finney in which the joint effects of drugs are compared under the hypotheses of additive effects and non-additive effects [8]. Proportions of patients who had achieved hypnosis with each treatment were converted to logits and the following additive model fitted to the data:

$$Y = \beta_0 + \beta_1 \log(T + (P \cdot M)) \quad (1)$$

where Y = logit transformed response; T = dose of propofol (mg kg^{-1}); M = dose of midazolam (mg kg^{-1}); P = relative potency at the appropriate effect level; β_0 and β_1 = variables to be estimated. By multiplying the dose by the relative potency, the former is converted into the "equivalent" dose of propofol; thus the term $T + (P \cdot M)$ may be thought of as "total propofol equivalents". Analogously, the term $M + (T/P)$ may be considered as "total midazolam equivalents" denoted by M_e, and is given by:

$$\log(P) = \beta_2 + \beta_3 \log(M_e) \quad (2)$$

where $M_e = M + (T/P)$.

The following model describing non-additive behaviour was also fitted to the data:

$$Y = \beta_0 + \beta_1 \log(T + P \cdot M + \beta_4 (T \cdot P \cdot M)^{0.5}) \quad (3)$$

where β_4 is analogous to Finney's coefficient of synergism.

Combinations of the drugs were considered to be non-additive if equation (3) fitted the data significantly better than equation (1).

The nature of the propofol–midazolam interaction for anaesthesia was examined by testing for a horizontal shift in the propofol log(dose)–response curve in the presence of midazolam. For this, the proportions of patients anaesthetized at each dose were converted to logits, and log(dose)–logit(response) curves were fitted by weighted least squares using SPSS-X [10]. $P \leqslant 0.05$ was regarded as significant.

RESULTS

There were no significant differences in age or weight of patients among the three treatment groups. The mean ages of patients receiving midazolam, propofol and the combination respectively were 31.6, 30.5 and 30.5 yr and mean (SD) weights 51.0 (9.4), 50.3 (7.7) and 50.7 (8.3) kg. The proportions of patients that achieved hypnosis and anaesthesia after each dose of propofol and midazolam are listed in table I.

The propofol dose–response curves for hypnosis and anaesthesia are presented in figure 1. The ED_{50} for hypnosis was 1.01 mg kg^{-1} and that for anaesthesia 1.93 mg kg^{-1}. The midazolam dose–response curve for hypnosis is presented in figure 2. The ED_{50} for hypnosis was 0.14 mg kg^{-1}. No patient became anaesthetized in the midazolam group with the doses used.

The dose–response curve for hypnosis using the combination of propofol and midazolam was compared with the dose–response curves for the two individual agents (fig. 3). The doses of propofol and propofol–midazolam combination were expressed as midazolam equivalents, in order that the curves for propofol and midazolam when used individually lay along the same line. The combination acted synergistically ($P < 0.01$), the coefficient of synergism being 0.78. This suggests that a dose of midazolam 0.1 mg kg^{-1} combined with a hypnotically equi-effective dose of propofol (0.79 mg kg^{-1}) gave a response equivalent to midazolam 0.278 mg kg^{-1} ($0.1 + 0.1 + 0.078 = 0.278$) rather than midazolam 0.2 mg kg^{-1} as would be expected if the drugs were additive. Another way of expressing this is that, when the combination was used in equi-effective doses, 85% of patients went to sleep using a total dose equivalent to that which put only 50% of patients to sleep using each agent individually.

The dose–response curves of propofol and the midazolam–propofol combination for anaesthesia are shown in figure 4. The addition of midazolam shifted the curve to the left ($P < 0.01$). The dose of propofol required to anaesthetize 50% of

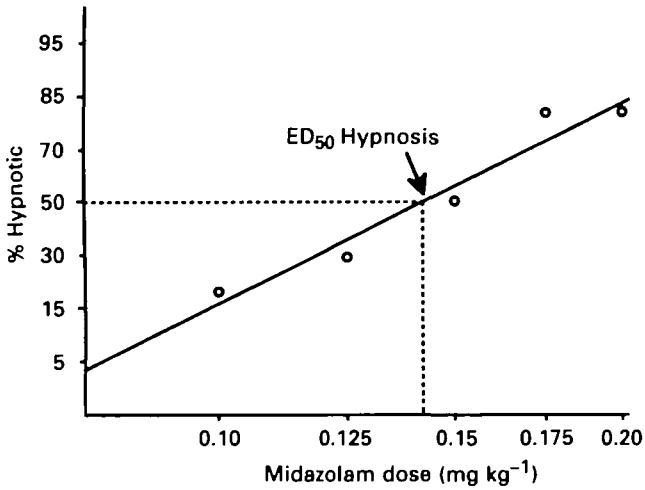

FIG. 2. Hypnotic (log)dose–(probit)response relationship for midazolam. The ED_{50} for hypnosis was 0.14 mg kg^{-1}. No patient achieved anaesthesia in the dose range used.

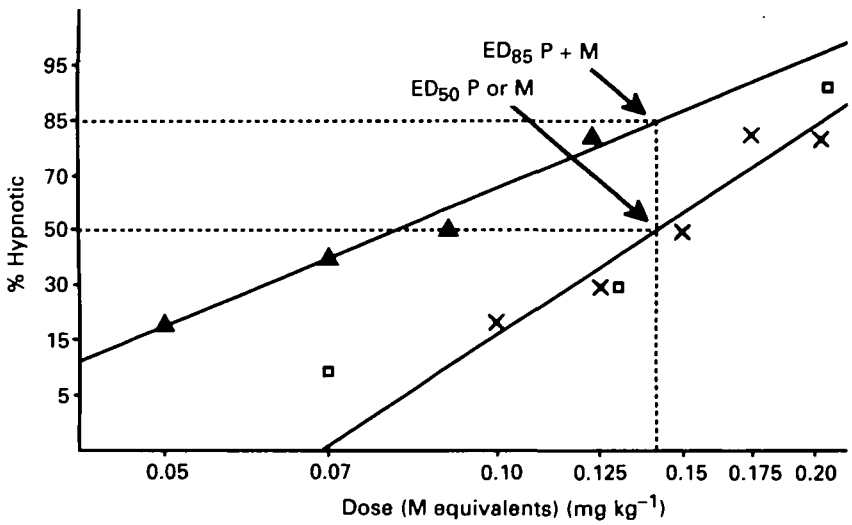

FIG. 3. (Log)dose–(probit)response curve for hypnosis of the propofol–midazolam (P + M) combination (▲) compared with dose–response curves for the two individual agents (× = midazolam (M); □ = propofol (P)). Doses of propofol and propofol–midazolam combination have been converted to "midazolam equivalents". The curve for the combination is shifted significantly to the left, indicating a synergistic interaction ($P < 0.01$). With the combination 85% of patients achieved hypnosis using a total dose equivalent to that which achieved hypnosis in 50% of patients using either agent individually.

patients was reduced from 1.93 mg kg^{-1} to 0.93 mg kg^{-1}, with the addition of midazolam 0.13 mg kg^{-1} at this point.

Arterial pressure measurements were analysed only up to the time of assessment of hypnosis and anaesthesia, because of the changes in arterial pressure caused by these assessments and the variable stimuli applied depending upon the degree of sedation. A decrease in systolic, diastolic and mean arterial pressure occurred in all three treatment categories ($P < 0.01$), but there was no correlation between increasing dose and the magnitude of change in arterial pressure for midazolam, propofol or the combination. The maximum decrease in mean arterial pressure occurred at 2 min for all three treatments (table I). Comparing the three treatments at similar doses based on their hypnotic potency (proportion

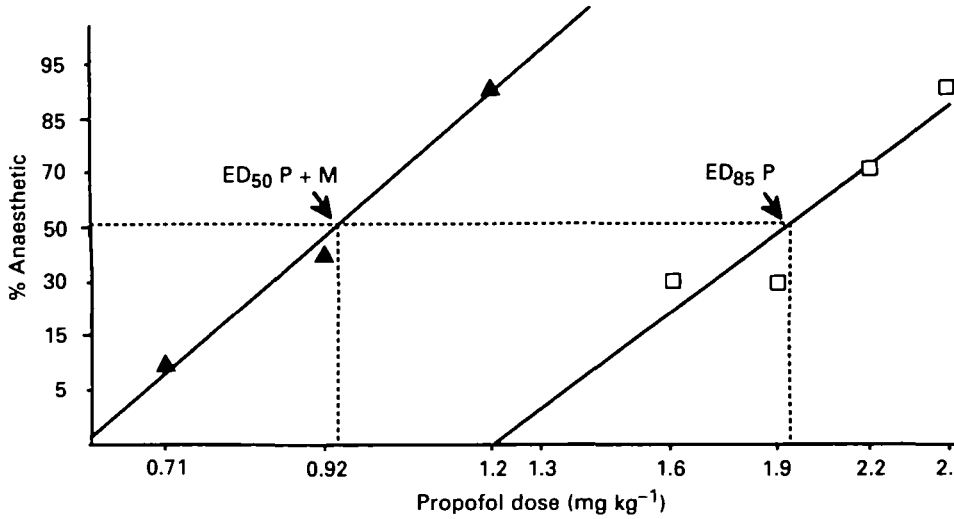

FIG. 4. Anaesthesia (log)dose–(probit)response curves of propofol (P) alone (□) and when combined with hypnotic doses of midazolam (P + M). (▲) The curve for the combination is shifted significantly to the left ($P < 0.001$). The addition of midazolam 0.13 mg kg^{-1} reduced the dose of propofol required to achieve anaesthesia in 50% of patients from 1.93 to 0.93 mg kg^{-1}.

hypnotic from 0.1 to 0.9) there were no differences in the decrease in arterial pressure among the three treatments. Comparing the changes in arterial pressure produced by propofol with the midazolam–propofol combination for anaesthesia on the same basis, there was again no difference between the two treatments.

DISCUSSION

The ED_{50} values for hypnosis of 1.01 mg kg^{-1} for propofol and 0.14 mg kg^{-1} for midazolam are comparable to previously reported values [1, 11–13]. There are no comparative data available for the end-point of anaesthesia as used in this study. With the combination, the coefficient of synergism was 0.87, corresponding to an ED_{50} 44% less than that expected if the drugs were simply additive. Although we were unable to demonstrate any anaesthetic action of midazolam in the doses used, a dose approximately equal to its ED_{50} for hypnosis caused a 52% increase in the anaesthetic potency of propofol. Thus, in the presence of propofol, midazolam acted as an equi-effective anaesthetic agent.

These results parallel closely those found for thiopentone–midazolam combination reported previously. A similar shift in the dose–response curve for anaesthesia was observed and similar synergism found for hypnosis [1]. However, the coefficient of synergism was larger in the present study: 0.87, compared with 0.37 for thiopentone–midazolam.

The reasons for the synergism observed are not clear, as little is known about the mechanism by which propofol causes sedation and anaesthesia. In a comparative study of the effects of ketamine, alphaxalone–alphadolone, methohexitone and propofol on synaptic excitations and inhibitions in the spinal cords of decerebrate cats, propofol was found to increase amplitude and time course of dorsal root potentials (DRP) in a manner similar to, but to an extent less than, methohexitone and alphaxalone–alphadolone. Propofol also depressed polysynaptic reflexes in a manner similar to ketamine [14]. The potentiation of DRP is thought to be a $GABA_A$ receptor mediated effect. It is not known what mechanism is involved with depression of polysynaptic reflexes, but this is an effect seen only weakly with barbiturates. Propofol has been shown also to potentiate duration of sleep and depth of anaesthesia in brain noradrenaline-depleted rat pups; this effect is also similar to that seen with barbiturates [15]. Although it has been postulated that these drugs produce an anaesthetic state via noradrenergic pathways, because there are $GABA_A$ receptors present as inhibitory components on noradrenergic pathways it is possible that this effect is also a $GABA_A$ receptor effect, reflecting GABA

predominance in the absence of significant noradrenergic discharge [16]. These studies provide circumstantial evidence of a role for $GABA_A$ receptors in mediating sedation caused by propofol and suggest some similarities between the effects of barbiturates and propofol in the brain.

The sedative effects of benzodiazepine agonists such as midazolam are mediated by interaction with the benzodiazepine receptor component of the $GABA_A$ receptor complex. Receptor occupancy by a benzodiazepine agonist causes an increase in the affinity of the inhibitory neurotransmitter GABA for its receptor, leading to potentiation of GABA-mediated chloride conductance and neuronal inhibition [17, 18]. Benzodiazepines also have actions similar to, but probably less pronounced than, those described for propofol in the spinal cord and in noradrenergic pathways [18].

The possibility that the observed synergism was caused by alterations in drug disposition cannot be excluded as the pharmacokinetic profile of propofol has not been studied in the presence of midazolam. Such an interaction was found for propofol and fentanyl, where a 50% increase in the mean arterial concentrations of propofol in the presence of fentanyl 100 μg was observed [19]. However, a more recent, slightly larger study has failed to confirm this finding [20] and it was suggested that the findings of the original study resulted from analysing data from a small number of subjects with widely variable pharmacokinetic profiles. Another problem with suggesting the observed synergism was caused by a pharmacokinetic interaction is that such an explanation does not explain why midazolam acted as if it were an anaesthetic agent when combined with propofol.

Arterial pressure was assessed only for a short interval after induction and this may account for the lack of correlation between dose of drug and degree of hypotension. However, the similar decrease in arterial pressure observed with the combination as with equipotent sedative doses of the individual drugs indicates that synergism extended to the hypotension that occurred at induction of anaesthesia.

In summary, we have shown that the combination propofol–midazolam is synergistic when used in the commonly accepted dose range. For hypnosis, using the combination, a 44% reduction in the ED_{50} of each agent individually was found and for anaesthesia the addition of midazolam 0.13 mg kg^{-1} caused a 52% reduction in the dose of propofol required. The results are similar to those found for a thiopentone–midazolam combination and are consistent with postulated actions for propofol at $GABA_A$ receptors. The combination may prove useful for sedation, induction and maintenance of anaesthesia.

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