

## Pharmacokinetic interactions between midazolam and propofol: an infusion study

J. TEH, T. G. SHORT, J. WONG AND P. TAN

### SUMMARY

*We have tested the hypothesis that the synergistic interaction which occurs when midazolam and propofol are combined for i.v. sedation is caused by an increase in the free plasma concentration of one of the drugs. Six patients undergoing general anaesthesia received an infusion of propofol with the addition of an infusion of midazolam commenced 30 min later. Another six patients received an infusion of midazolam with the addition of an infusion of propofol 30 min later. All infusions were administered via pharmacokinetic model-controlled syringe pumps programmed to maintain a constant plasma concentration. Venous blood samples were taken before and after introduction of the second infusion for later analysis. Free plasma concentration of midazolam increased from 2.0 (SD 1.5) ng ml<sup>-1</sup> to 2.2 (1.9) ng ml<sup>-1</sup> after introduction of the propofol infusion ( $P = 0.32$ ). Free propofol plasma concentration was unchanged at 18.5 (5.3) ng ml<sup>-1</sup> before and 18.7 (7.8) ng ml<sup>-1</sup> after introduction of the midazolam infusion ( $P = 0.94$ ). It was concluded that the observed synergism with this combination cannot be explained solely by alteration in free plasma concentration of either of these drugs when they are administered together. (Br. J. Anaesth. 1994; 72: 62–65)*

### KEY WORDS

Anaesthetics, i.v.: propofol. Hypnotics, benzodiazepine: midazolam. Pharmacology: drug interactions.

When i.v. sedatives are administered simultaneously, synergism between them is common and has been the subject of editorial comment [1, 2]. Two studies have found that, when midazolam and propofol were administered simultaneously, the ED<sub>50</sub> for the combination was approximately 45% less than expected from the ED<sub>50</sub> values of the individual agents [3, 4]. The mechanism of this synergism has not been determined, and although it is thought to result from pharmacodynamic interactions occurring at a receptor level in the brain, a pharmacokinetic cause for the synergism has not been excluded. In this study, we have tested the hypothesis that the synergistic interaction which occurs when midazolam and propofol are administered together is caused by an increase in the free plasma concentration of one of the drugs.

### PATIENTS AND METHODS

The study was approved by the Research Ethics Committee of the Faculty of Medicine, The Chinese University of Hong Kong. We studied 12 adult Chinese patients (aged 18–60 yr) who gave written informed consent. All were ASA class I or II, within 20% of ideal body weight and undergoing elective surgical procedures not associated with significant blood loss. Patients with a history of recent ingestion of psychotropic medication, known sensitivity to benzodiazepines or propofol, pregnancy or anaemia were excluded. Patients were allocated randomly to one of two treatment groups.

All patients were unpremedicated. Anaesthesia was induced with i.v. fentanyl 1.5 µg kg<sup>-1</sup>, thiopentone 3–5 mg kg<sup>-1</sup> and atracurium 0.5 mg kg<sup>-1</sup>. The trachea was intubated and ventilation controlled to maintain normocapnia. Anaesthesia was maintained with 70% nitrous oxide in oxygen, incremental doses of atracurium as indicated by a neuromuscular block monitor and an infusion of either propofol or midazolam. An 18-gauge i.v. cannula placed in a large forearm vein was used for administration of all drugs. A second 18-gauge i.v. cannula placed near the antecubital fossa of the opposite forearm was used for blood sampling.

One group of six patients received an infusion of propofol to maintain a constant plasma concentration of 1504 ng ml<sup>-1</sup>. After 30 min (a time chosen to ensure steady state plasma concentrations had been achieved) a concurrent infusion of midazolam was also commenced to maintain a constant plasma concentration of 94 ng ml<sup>-1</sup>. A second group of six patients received the midazolam infusion first, followed 30 min later by a concurrent infusion of propofol. The infusions were administered by computer-controlled infusion pumps (Ohmeda 9000, Medishield, U.K.), connected to 386SX IBM-compatible laptop computers via an RS232C serial interface. Previously published pharmacokinetic algorithms and variables for adult patients were used to deliver the steady state infusions [5,6]. The plasma concentrations chosen were those predicted by the pharmacokinetic model to have been achieved

J. TEH, M.B., B.S.; T. G. SHORT, M.D., F.A.N.Z.C.A.; J. WONG, M.B., B.S.; P. TAN, B.SC.CHEM.; Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Accepted for Publication: July 21, 1993.

Correspondence to T.G.S.

by the ED<sub>50</sub> doses for hypnosis for the combination in a previous paper describing the synergistic interaction (midazolam 0.14 mg kg<sup>-1</sup> and propofol 1.01 mg kg<sup>-1</sup>) [3].

Two 5-ml venous blood samples were obtained at 2-min intervals for 10 min before infusion of the second drug was commenced and for 10 min after that commencement. Plasma concentrations of midazolam and propofol were analysed by high pressure liquid chromatography using techniques previously described [6, 7]. Protein binding was assessed on every sample using equilibrium dialysis.

Plasma samples for the midazolam assay were stored at -70 °C. Calibration graphs were linear over the range 10-500 ng ml<sup>-1</sup>. The within-day coefficient of variation of the assay varied between 6.8% at 10 ng ml<sup>-1</sup> to 4.5% at 500 ng ml<sup>-1</sup>; the limit of accuracy was 10 ng ml<sup>-1</sup>. Protein binding was measured by equilibrium dialysis (Spectra/Por, Spectrum, Texas, U.S.A.) using Spectra/Por 2 dialysis membranes with a molecular weight cut-off of 12000-14000. The reagent was Sorensen's phosphate buffer (pH 7.40). Samples were dialysed against phosphate buffer 1 ml for 5 h in a 37 °C water bath. After dialysis, both plasma and buffer fractions were analysed separately for their midazolam content. The within-day coefficient of variation for the protein binding assay was 2.7%. Because free midazolam concentrations were less than the limit of accuracy of the assay, it was necessary to spike each sample with a known quantity of midazolam (500 µg) for assessment of protein binding.

Whole blood samples for the propofol assay were stored at 4 °C. Calibration graphs were linear over the range 2-3000 ng ml<sup>-1</sup>. The between-batch coefficient of variation of the assay was 6.7% at 50 ng ml<sup>-1</sup> and 4.0% at 3000 ng ml<sup>-1</sup>. The limit of accuracy of the assay was 2 ng ml<sup>-1</sup>. Protein binding of propofol was also determined by equilibrium dialysis (Spectra/Por, Spectrum, Texas, U.S.A.) using Spectra/Por 2 dialysis membranes with a molecular weight cut-off of 12000-14000. The reagent was Sorensen's phosphate buffer (pH 7.40). Samples were dialysed against phosphate buffer 1 ml for 5 h in a 37 °C water bath. After dialysis, both plasma and buffer fractions were analysed separately for their propofol content. The within-day coefficient of variation for the protein binding assay was 5.0%.

Linearity of the infusion up to the time of introduction of the second drug was assessed by analysis of variance for repeated measures. The

mean free plasma concentrations of the six samples taken before commencement of the second drug infusion were compared with the mean free plasma concentration of the five samples taken after introduction of the second drug infusion, using a two-tailed paired Student's *t* test. Using six subjects, the power of the study was 0.8 for the detection of an 80% increase in free concentration of each drug [8]. This is the approximate change in free concentration required to explain the previously observed 44% decrease in the hypnotic ED<sub>50</sub> when using the combination. *P* < 0.05 was regarded as significant.

RESULTS

Free plasma concentrations measured for the group who received a midazolam infusion first are displayed in figure 1; mean data are listed in table I. Mean age of the patients was 32 yr (range 18-46 yr) and weight 59 kg (range 47-71 kg); there were four females and two males. On testing the midazolam infusion for linearity during the 10-min observation period before introduction of the propofol, there was no significant within-subject change in free midazolam concentration (*P* > 0.05). The mean midazolam concentration maintained during the 20-min study was 84 ng ml<sup>-1</sup>. Although free midazolam plasma concentration increased by 20% after the propofol infusion was commenced, there was no statistically

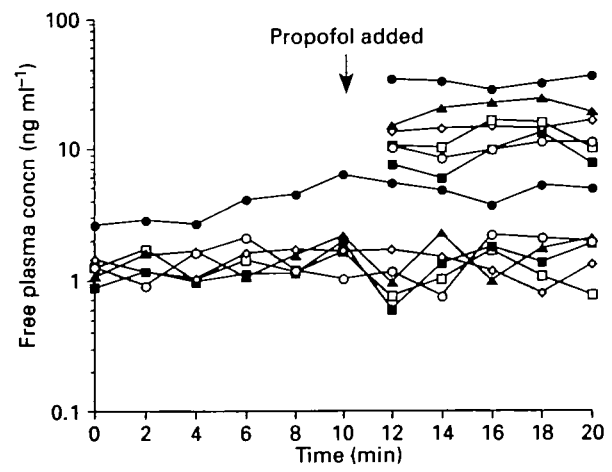


FIG. 1. Free plasma concentrations of midazolam during steady-state infusion. An infusion of propofol was commenced concurrently after 10 min.

TABLE I. Mean (SD) free plasma concentrations and free fraction of midazolam and propofol before and after infusion of the second drug. For the midazolam group the second infusion was propofol and for the propofol group the second infusion was midazolam

	Before second drug	After second drug	<i>P</i>
Midazolam group			
Free plasma concn (ng ml <sup>-1</sup> )	2.0 (1.5)	2.2 (1.9)	0.32
Free fraction (%)	2.29 (0.89)	2.23 (1.06)	0.56
Propofol group			
Free plasma concn (ng ml <sup>-1</sup> )	18.5 (5.3)	18.7 (7.8)	0.94
Free fraction (%)	1.4 (0.30)	1.4 (0.50)	0.83

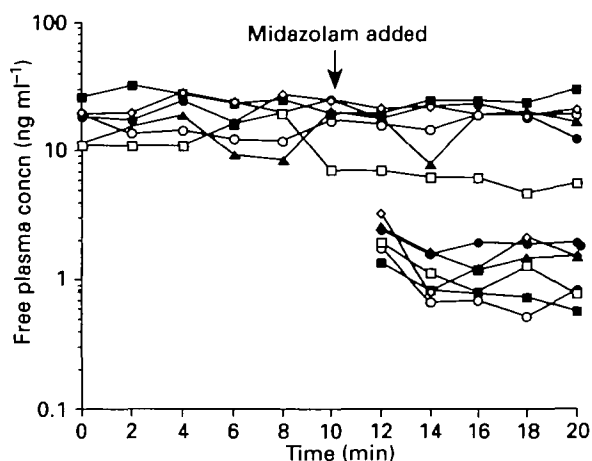


FIG. 2. Free plasma concentrations of propofol during steady state infusion. An infusion of midazolam was commenced concurrently after 10 min.

significant difference in mean free midazolam plasma concentrations ( $P = 0.32$ ).

Plasma concentrations measured for the group who received a propofol infusion first are displayed in figure 2; mean data are listed in table I. The mean age of patients in this group was 40 yr (range 19–60 yr) and weight 54 kg (range 48–65 kg); there were two females and four males. On testing the propofol infusion for linearity during the 10-min observation period before introduction of the midazolam, there was no significant within-subject change in free midazolam concentration ( $P > 0.05$ ). The mean plasma concentration of propofol maintained during the 20-min study was  $1304 \text{ ng ml}^{-1}$ . There was no statistically significant difference in mean free propofol plasma concentrations before and after commencing the infusion of midazolam ( $P = 0.94$ ).

#### DISCUSSION

In the present study, the free plasma concentration of midazolam increased by 20% after introduction of a propofol infusion and the free plasma concentration of propofol was unchanged after introduction of a midazolam infusion. However, no statistically significant alterations in the free plasma concentrations of either midazolam or propofol were found that would account for the synergism observed when these drugs are combined for i.v. induction of anaesthesia.

The format of examining steady-state free plasma concentrations rather than plasma concentrations after bolus doses was chosen because it avoided problems associated with measuring plasma concentrations accurately at a time when they are changing rapidly and allowed patients to act as their own controls. Past studies that have used a bolus dose format to study pharmacokinetic interactions have produced conflicting results because of these problems [9, 10]. The use of patients under general anaesthesia was chosen because, although several drugs other than the test drugs were administered also to the patients, this would be the case in a clinical situation. The likelihood of observing an increase in free fraction by displacement from

protein binding sites would have been increased with this format. The plasma concentrations chosen were in the range in which synergism has been observed in past clinical studies using bolus doses. Although this made it necessary to spike the midazolam samples to measure the protein binding, this should have again increased the likelihood of a displacement reaction in the presence of propofol—an effect that was not observed. Spiking of samples has been used in the past for the assessment of protein binding of midazolam and protein binding has been shown to be independent of total midazolam concentration up to  $10000 \text{ ng ml}^{-1}$  [11].

Free drug concentrations were measured only in the plasma and so a change in free concentration in the cerebrospinal fluid or brain extracellular fluid has not been excluded by this study. However, because it is the free concentration in the plasma which drives the drug concentration in the brain, this is unlikely to occur. In addition, when whole brain concentrations of morphine and midazolam were measured in rats, there was no evidence of an alteration in concentration of each agent that would account for the synergistic interaction observed with this combination [12]. It is more likely that the synergism observed between propofol and midazolam was the result of pharmacodynamic interactions occurring at the receptor level in the brain, as both drugs are thought to exert effects on GABA<sub>A</sub> receptors in the brain. Possible interactions that may occur between these drugs at the GABA<sub>A</sub> receptor have been discussed previously [3]. The power of the study was sufficient only to exclude the hypothesis that the observed synergism is solely caused by an alteration in free concentration of one of the drugs. The possibility that a smaller alteration in free concentration is part of the reason for synergism is not excluded.

In conclusion, we found no statistically significant alteration in the free plasma concentration of either midazolam or propofol that would explain the synergistic interaction observed when these drugs are combined for i.v. sedation.

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