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HYPNOTIC AND ANAESTHETIC INTERACTIONS BETWEEN MIDAZOLAM, PROPOFOL AND ALFENTANIL

T. G. SHORT, J. L. PLUMMER AND P. T. CHUI

SUMMARY

We have examined interactions between midazolam, propofol and alfentanil using two end-points of light sedation (hypnosis) and anaesthesia. Quantal dose–response curves were determined in 400 female patients for the drugs individually and in combination. At the hypnotic end-point, interactions were analysed by fitting the data to a mathematical model where the response depended on the doses of the three drugs with additional terms included to describe non-additive interactions of the various combinations of the three drugs. There were significant interactions for hypnosis; the decrease in expected ED_{50} for the various combinations were: midazolam–propofol = 37%, midazolam–alfentanil = 46%, propofol–alfentanil = 20%, midazolam–propofol–alfentanil = 42%. Whilst all responses to the two-drug combinations were synergistic, the three-drug combination led to a response that was less than that expected from the effects of the individual agents and their two drug interactions. For anaesthesia, dose-related effects could not be demonstrated for midazolam or alfentanil when used alone. The decrease in ED_{50} of propofol in the presence of the other compounds was propofol–midazolam = 52%, propofol–alfentanil = 73%, propofol–midazolam–alfentanil = 82%. When comparing the different combinations, the responses varied markedly at each end-point assessed and could not be predicted from the responses of the individual agents.

KEY WORDS

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

Administration of multiple drugs which have similar effects is common in anaesthesic practice. Among i.v. sedative agents the following paired combinations have been studied in humans and their interactions quantitated: thiopentone–midazolam [1, 2], thiopentone–propofol [3], methohexitone–midazolam [4], propofol–midazolam [5, 6], propofol–alfentanil [7], midazolam–fentanyl [8] and midazolam–alfentanil [9, 10]. With the exception of propofol–alfentanil which was additive, the combinations have been shown to interact in a synergistic manner. It is not known if this synergism extends to combinations of more than two sedatives or if a ceiling exists to the degree of synergism obtainable.

In this study we examined the interactions between midazolam, propofol and alfentanil at two end-points that correspond to light sedation (loss of response to verbal command) and anaesthesia (loss of response to a noxious stimulus).

PATIENTS AND METHODS

We studied 400 Chinese female patients undergoing elective gynaecological surgery. 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 and gave informed consent. Approval was obtained from the Research Ethics Committee of the Chinese University of Hong Kong.

The study was conducted in three parts over a 10-month period. In the first part of the study, dose–response relationships were established for midazolam, propofol and alfentanil administered individually in the patient population. Ten patients were allocated randomly to receive one of five doses of midazolam or alfentanil or one of seven doses of propofol. The drugs were injected over 10 s into a forearm vein followed by a 10-ml flush of physiological saline. In the second part of the study, the combination of midazolam and propofol was studied, then in the third part, the combinations midazolam–alfentanil, propofol–alfentanil and midazolam–propofol–alfentanil. Results for interactions with the midazolam–propofol combination have been reported previously [5].

Patients were assessed for hypnosis and anaesthesia 4 min after midazolam and 2 min after propofol or alfentanil injection, these times being the approximate times to peak effect of the two drugs when given as an i.v. bolus. The observer was blind to the dose given. Hypnosis was defined as failure to open the eyes on verbal command. In those patients who achieved hypnosis, anaesthesia was defined as failure to respond to a standard 5-s transcutaneous tetanic stimulus (50-Hz, 80-mA, 0.25-ms pulses)

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over the ulnar nerve—an end-point shown to be suitable for determination of MAC for volatile anaesthetic agents [11].

For the paired drug combinations, a constant ratio of the ED_{50} values for hypnosis was used. Beginning with 50% of the ED_{50} values, several doses both greater and smaller than this were chosen, whilst maintaining the dose ratio constant. Midazolam was administered 2 min before either propofol or alfentanil and another 2 min was allowed before assessment. When both propofol and alfentanil were given, alfentanil was given first. For the three-drug combination 33% of the ED_{50} for the individual drugs was chosen as the initial dose ratio and then we used methodology similar to that used for the paired combinations. The doses are shown in table II.

Statistical analysis

Analysis of variance was used to compare age and weight in patient groups. Patients in each of the three phases of the study were compared similarly. ED_{50} values were calculated by maximum likelihood. At the hypnotic end-point the three drugs were examined for interactions by an extension of the method described by Plummer and Short [12] for two drugs. Data points where 0% or 100% of the subjects achieved hypnosis or anaesthesia were not used. The following model was fitted to the remaining data by weighted least squares:

$$\log(p_i) = \beta_0 + \beta_1 \log(A_i + P_{Bi} B_i + P_{Ci} C_i + \beta_6 (A_i P_{Bi} B_i)^{1/2} + \beta_7 (A_i P_{Ci} C_i)^{1/2} + \beta_8 (P_{Ci} P_{Bi} C_i B_i)^{1/2} + \beta_9 (A_i P_{Bi} B_i P_{Ci} C_i)^{1/3}) \quad \text{(Model 1)}$$

where p_i = proportion of subjects who went to sleep at the ith dose, and A_i, B_i and C_i = the amounts of propofol, midazolam and alfentanil, respectively, at the ith dose. P_{Bi} and P_{Ci} represent the relative potencies of midazolam and alfentanil, respectively, to propofol at the ith dose, and are given by:

$$P_{Bi} = e^{\beta_2 + \beta_3 \log A_i'} \quad (1)$$

$$P_{Ci} = e^{\beta_4 + \beta_5 \log A_i'} \quad (2)$$

where A_i' = amount or propofol alone which, if drug effects were additive (in the sense of dose addition as defined by Smith [13]) would be equieffective with the total amount of drugs at the ith dose. A_i' is given as the solution to:

$$A_i' = A_i + B_i P_{Bi} + C_i P_{Ci} \quad (3)$$

The parameters β_0–β_9 define the relationship between the amounts of the three drugs and the responses. β_0–β_5 relate to slopes and intercepts of the log(dose)–response curves of the three drugs. β_6 relates to effects when both propofol and midazolam are present which cannot be explained on the basis of effects of the individual drugs (i.e. an interaction). Similarly, β_7 and β_8 relate to interactions between propofol and alfentanil, and midazolam and alfentanil, respectively. β_9 relates to a three-drug interaction (i.e. that part of the effect observed when all three drugs are present which cannot be explained on the basis of effects of the individual drugs and the pairwise interactions).

Model 1 was fitted to the data by least squares, using the mid-point and secant methods to solve equation (3) at each step [12]. The contribution of each term to the model was examined by excluding the terms, one at a time, and determining if the fit of the model deteriorated significantly. This was done by examining the increase in residual sum of squares after dropping of the term (approximate chi-square test), graphical analysis and examination of residuals. Fractional analysis was performed also, to provide an alternative method of data presentation that simplifies comparison with results from other studies.

For the end-point of anaesthesia an alternative approach was used because midazolam is not thought to be an anaesthetic, as defined as ability to suppress motor response to a 5-s tetanus when used in a clinically acceptable dose range [2]. The anaesthesia dose–response curves for midazolam, alfentanil and the midazolam–alfentanil combination were tested for parallelism and then for significant shift to the left in the presence of propofol by logistic regression using the Statistical Package for Social Sciences version 4.0. In the case of the midazolam–alfentanil combination, because the dose ratio was constant, the doses of the two drugs were combined and treated as a new drug.

RESULTS

There were no significant differences in mean age and weight among the groups (table I). Comparisons of mean age and weight of patients in the three phases of the study also revealed no differences among the groups: mean (SD) age for phases 1–3 were 31.4 (5.4), 30.6 (6.4), 32.1 (5.0) yr and weight 51.6 (10.3), 50.3 (8.3), 52.5 (9.2) kg. It was concluded that comparisons between patients in the three phases of the trial are valid. The proportions of patients that achieved hypnosis and anaesthesia in each dose category of the seven groups of patients are shown in table II.

For hypnosis, the ED_{50} midazolam values were: 0.14 mg kg^{-1}, propofol 1.06 mg kg^{-1} and alfentanil 0.094 mg kg^{-1} (fig. 1). Constant ratios of these values were used for the combinations. With the combinations the dose–response curves were all shifted to the left. In figure 2, all dose–response curves for hypnosis are shown: doses of propofol, alfentanil and the combinations have been converted to equivalent doses of propofol using equations (1) and (2). The dose–response curves for midazolam and alfentanil now lie on the same line as that for propofol. The ED_{50} values (confidence intervals) for the three drugs and the combinations are listed in table III.

Model 1 was found to be a good fit for the data, as assessed by graphical examination and analysis of residuals. Parameter estimates for this model are shown in table IV. A total of 280 patients contributed to the model (i.e. after excluding those data where either 0% or 100% of patients in the individual groups of 10 became hypnotic). Each interaction

TABLE I. *Mean (SD or range) age and weight of patients in the seven drug groups. M = midazolam, P = propofol, A = alfentanil. There were no significant differences between the groups*

Group	*n*	Age (yr)	Weight (kg)
M	50	31.6 (18–40)	51.0 (9.4)
P	70	30.4 (18–40)	51.0 (10.6)
A	50	32.7 (21–40)	53.1 (10.9)
M–P	80	30.6 (18–38)	50.3 (8.3)
M–A	50	31.8 (20–40)	54.1 (9.9)
P–A	50	31.9 (20–40)	54.1 (10.0)
M–P–A	50	32.6 (18–40)	52.2 (7.4)

term was examined for its contribution to the model and found to be necessary. When the three-drug interaction term was removed from the model, the reduced model was no longer a good fit. The change in residual sum of squares on removing this term was 3.35. An approximate hypothesis test made by referring this value to the chi-square distribution (1 d.f.) gave $P = 0.07$, providing some evidence of lack of fit of the reduced model. Examination of residuals of the reduced model provided compelling evidence of lack of fit; this model underestimated the response in 11 of the 12 two-drug combinations and grossly overestimated the response in all four of the three-drug combinations. It was concluded that a significant three-drug interaction occurred. Removing each pairwise drug interaction led to a significantly (> 3.84) increased sum of squares.

The three-drug interaction term was negative ($\beta_9 = -0.86$). This implies that the effects of the three drugs was less then expected from the effects of the individual drugs and the pairwise interactions, all of which were positive (synergistic). However, use of the three-drug combination still led to a significant shift of the dose–response curve to the left (synergism) compared with the individual drugs. The decrease in expected ED_{50} values for the combinations were midazolam–propofol = 37%, midazolam–alfentanil = 46%, propofol–alfentanil = 20% and midazolam–propofol–alfentanil = 42%. ED_{50} fractional analysis is shown in table V.

For the anaesthetic end-point, using the individual drugs, only propofol produced anaesthesia in the dose ranges chosen (ED_{50} 1.93 mg kg^{-1}). Anaesthesia was not expected with midazolam [2]. Alfentanil caused marked muscular rigidity which interfered

TABLE II. *Doses of midazolam, propofol and alfentanil used and the proportions of patients achieving hypnosis and anaesthesia for each dose category*

Midazolam (mg kg^{-1})	Propofol (mg kg^{-1})	Alfentanil (mg kg^{-1})	Proportion hypnotic	Proportion anaesthetized
0.1	0	0	0.2	0
0.125	0	0	0.3	0
0.15	0	0	0.5	0
0.175	0	0	0.8	0
0.2	0	0	0.8	0
0	0.7	0	0.1	0
0	1.0	0	0.3	0
0	1.3	0	0.9	0
0	1.6	0	1.0	0.3
0	1.9	0	1.0	0.3
0	2.2	0	1.0	0.7
0	2.5	0	1.0	0.9
0	0	0.05	0	0
0	0	0.075	0.3	0
0	0	0.10	0.5	0.2
0	0	0.125	0.9	0.2
0	0	0.15	1.0	0
0.03	0.21	0	0.2	0
0.04	0.29	0	0.4	0
0.05	0.36	0	0.5	0
0.065	0.46	0	0.8	0
0.085	0.60	0	1.0	0
0.10	0.71	0	1.0	0.1
0.13	0.92	0	1.0	0.4
0.17	1.2	0	1.0	0.9
0.035	0	0.025	0.4	0
0.044	0	0.031	0.7	0.1
0.056	0	0.040	0.9	0
0.070	0	0.049	0.9	0.6
0.085	0	0.061	1.0	0.7
0	0.25	0.025	0.1	0
0	0.31	0.031	0.3	0
0	0.4	0.041	0.4	0.1
0	0.5	0.049	0.8	0.6
0	0.63	0.062	0.9	0.7
0.023	0.17	0.016	0.3	0
0.030	0.21	0.021	0.6	0
0.037	0.26	0.026	0.8	0.1
0.047	0.33	0.032	0.9	0.5
0.059	0.42	0.041	1.0	0.8

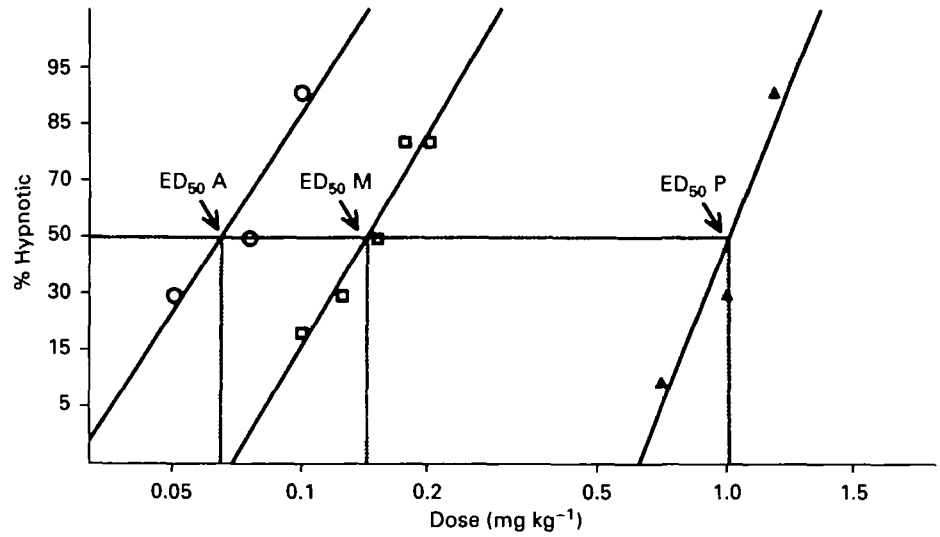

FIG. 1. Hypnotic (log)dose–(probit)response curves for midazolam (M) (□), propofol (P) (▲) and alfentanil (A) (○) when given alone.

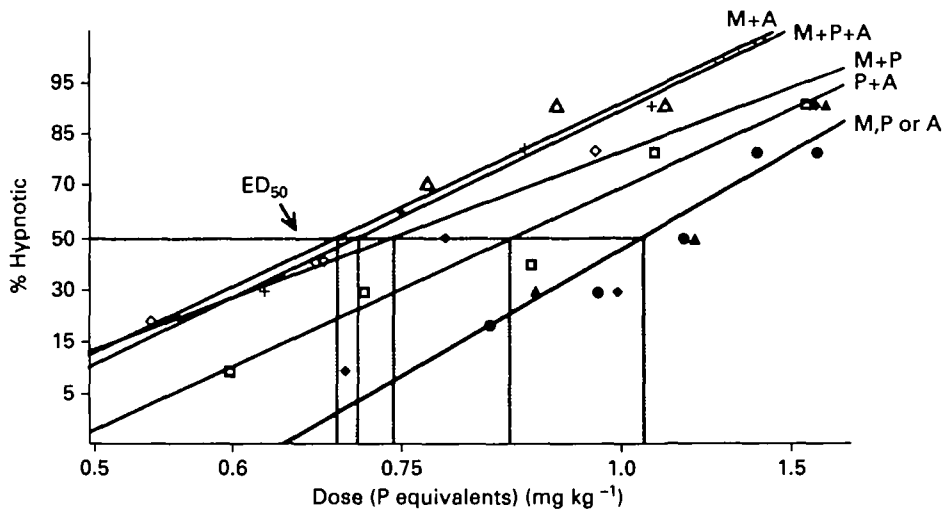

FIG. 2. Hypnotic (log)dose–(probit)response curves for midazolam (M) (●), propofol (P) (◆), alfentanil (A) (▲) and the combinations M+P (◇), M+A (△), P+A (□), M+P+A (+). M and A doses have been converted to P equivalents. The curves for M, P and A when given alone now lie along the same line.

TABLE III. *ED_{50} values and 95% confidence intervals (CI) for the individual drugs and the combinations for the hypnotic end-point. M = Midazolam, P = propofol, A = alfentanil*

Drug	ED_{50}	Lower CI	Upper CI
M	0.14	0.118	0.169
P	1.036	0.887	1.168
A	0.094	0.079	0.109
M–P	0.045–0.32	0.037–0.262	0.052–0.374
M–A	0.038–0.026	0.025–0.017	0.045–0.031
P–A	0.397–0.039	0.334–0.032	0.473–0.046
M–P–A	0.028–0.198–0.019	0.021–0.151–0.015	0.032–0.230–0.022

with reliable interpretation of responses when doses $\geqslant 0.1$ mg kg^{-1} were used; all but two patients appeared to move in response to the 5-s tetanus. The difficulties of interpretation of results in the presence of such muscular rigidity removed the opportunity to restart the first phase of the study using larger doses of alfentanil. The dose–response curves for propofol in the presence of midazolam, alfentanil and midazolam–alfentanil are shown in figure 3. In all three cases, there was a significant shift to the left, indicating synergistic interactions. The decrease in ED_{50} for the combinations were propofol–midazolam = 52%, propofol–alfentanil = 73%, propofol–midazolam–alfentanil = 82%. Alfentanil caused a greater reduction in ED_{50} at the anaesthetic end-point compared with the hypnotic end-point (73% *vs* 20%) whilst the effect of midazolam in reducing the propofol ED_{50} was less pronounced at the anaesthetic end-point compared with the hypnotic end-point (52% *vs* 37%) (table VI).

TABLE IV. *Parameter estimates for the 10-parameter model (Model 1). M = Midazolam, P = propofol, A = alfentanil. β_4–β_9 relate intercepts and slopes for M and A to those of P (see text)*

Parameter	Explanation	Estimate
β_0	Intercept P	−0.34
β_1	Slope P	5.84
β_2	Slope M	2.04
β_3	Intercept M	−0.57
β_4	Slope A	2.44
β_5	Intercept A	−0.39
β_6	M–P interaction	0.85
β_7	P–A interaction	0.42
β_8	M–A interaction	1.05
β_9	M–P–A interaction	−0.86

The anaesthetic ED_{50} for the midazolam–alfentanil combination was 0.068–0.048 mg kg^{-1}. This could not be compared directly with the ED_{50} values of the individual agents for anaesthesia because these could not be determined.

DISCUSSION

Interactions of the paired combinations at the hypnotic end-point were comparable to the findings of previous studies. For midazolam–propofol the interaction was of the same order of magnitude as that found by McClune, McKay and Clarke [6]. For midazolam–alfentanil, the algebraic sum was identical to that found by Vinik, Bradley and Kissin (0.54) [9]. Although alfentanil 0.02 mg kg^{-1} has been found previously not to potentiate significantly the hypnotic action of propofol [7], the mean induction dose of propofol was decreased from 1.1 to 0.9 mg kg^{-1} in that study, which is of similar magnitude to the algebraic fraction of 0.80 in the

TABLE V. *ED_{50} fractional analysis for hypnotic end-point. M = Midazolam, P = propofol, A = alfentanil*

	Component						
	Midazolam		Propofol		Alfentanil		Sum of fractions
Drug	Dose	Fraction	Dose	Fraction	Dose	Fraction	
M	0.143	1	—	—	—	—	1
P	—	—	1.059	1	—	—	1
A	—	—	—	—	0.094	1	1
M–P	0.046	0.322	0.328	0.310	—	—	0.63
M–A	0.037	0.259	—	—	0.026	0.277	0.54
P–A	—	—	0.403	0.381	0.039	0.415	0.80
M–P–A	0.028	0.196	0.197	0.186	0.019	0.202	0.58

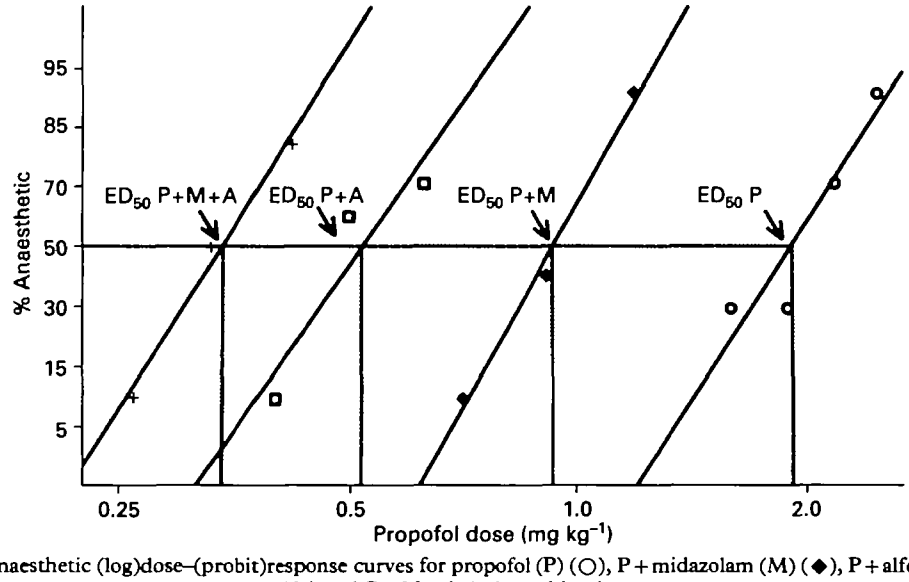

FIG. 3. Anaesthetic (log)dose–(probit)response curves for propofol (P) (○), P + midazolam (M) (◆), P + alfentanil (A) (□) and P + M + A (+) combinations.

TABLE VI. *Change in ED_{50} of propofol and 95% confidence intervals (CI) for anaesthetic end-point in the presence of midazolam (M), alfentanil (A) and M + A, dose of M, A, M + A given at this point and % change in ED_{50} of P. P value is comparison with propofol alone*

Drug	ED_{50} P	95% CI	Dose M/A (mg kg^{-1})	ED_{50} P (% decrease)	*P*
P	1.97	1.79–2.17			
P–M	0.95	0.85–1.08	0.13/0	52	< 0.01
P–A	0.52	0.045–0.067	0/0.05	73	< 0.001
P–M–A	0.375	0.33–0.43	0.048/0.033	82	< 0.001

present study. The difference in statistical significance is caused by the number of patients studied: 50 in the study by Vinik, Bradley and Kissin compared with 110 patients in the present study. The degree of synergism observed between propofol and alfentanil was considerably less than for combinations which included midazolam.

For the three-drug interaction, a negative coefficient of -0.87 was found. This implies that the three-drug combination did not produce as much sedation as expected from the combined doses of the individual agents and the pairwise interactions. Using fractional analysis, the fraction was 0.58, indicating a 42% decrease in total dose compared with individual use of the drugs. It is apparent that no further synergism occurred beyond that observed for the pairwise combinations.

For anaesthesia, the lack of an ED_{50} value for midazolam and alfentanil when given alone implied that only the shift to the left in the dose–response curve for propofol in the presence of midazolam, alfentanil or the combination could be tested for statistical significance. The effects of the combinations cannot be quantitated as for the hypnotic end-point. The shift to the left was significant in all cases, with the three-drug combination showing the greatest degree of synergism followed by propofol–alfentanil, and propofol–midazolam showing the least. Compared with the hypnotic end-point, combinations which included alfentanil caused the greatest decrease in ED_{50}. The propofol–alfentanil combination caused effects similar to those observed with thiopentone and alfentanil by Mehta, Bradley and Kissin [14] where the effect of alfentanil on thiopentone dose was also much more profound for suppression of response to a noxious stimulus than for suppression of response to verbal command.

Opioids are not thought to be true anaesthetic agents when used alone, as indicated by the incidence of awareness with high dose opioid techniques of anaesthesia [15, 16]. The common practice of adding small doses of a benzodiazepine such as midazolam when using high dose opioid techniques is supported by the results for the midazolam–alfentanil combination. Modest doses of this combination suppressed response to a noxious stimulus, whilst relatively large doses of the individual agents in the first part of the study proved inadequate for determination of individual ED_{50} values. Because the ED_{50} for anaesthesia of the individual agents must be greater than $0.2\ mg\ kg^{-1}$ for midazolam and $0.15\ mg\ kg^{-1}$ for alfentanil, by implication a very large degree of synergism occurred with this combination. The ability of modest doses of the midazolam–alfentanil combination to eliminate responsiveness to a noxious stimulus has a parallel in the observation of significant hypotensive effects from use of the combination of diazepam and fentanyl [17] in premedicated cardiac surgery patients when compared with use of each agent alone. The interaction appears to be specific to the combination of an opioid with a benzodiazepine.

The degree of synergism observed with the combinations varied markedly between the two sedative end-points and could not be predicted from the behaviour of the drugs alone. This indicates that when using combinations of sedatives such as those used in this study, the combination should be regarded as a new "drug" with individual properties, rather then merely reflecting the known properties of the individual agents.

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