

Hypnotic and Anesthetic Interactions between Ketamine and Midazolam in Female Patients

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Background: Midazolam, if used with ketamine for induction and maintenance of anesthesia, may attenuate hyperdynamic circulatory effects and prevent undesirable emergent reactions. The nature of the interaction between midazolam and ketamine used for anesthesia induction was studied in female patients.

Methods: Quantal dose-response curves were determined in 170 female patients for the drugs, individually and in combination. Two endpoints were assessed, loss of response to verbal command (hypnosis) and loss of response to a 5-s transcutaneous tetanus (anesthesia). At the hypnotic endpoint, interactions were analyzed by fitting the data to a mathematical model in which the response was analyzed in terms of the doses of the two drugs, and an additional term was included to describe nonadditive interactions. At the anesthetic endpoint, the decrease in ED₅₀ of ketamine in the presence of midazolam was assessed because dose-related effects could not be demonstrated for midazolam alone.

Results: At the hypnotic endpoint, the ED₅₀s were: 0.15 mg/kg midazolam (95% CIs 0.11–0.38 mg/kg), 0.37 mg/kg ketamine (95% CIs 0.08–0.44 mg/kg), and the combination of 0.086 mg/kg midazolam and 0.27 mg/kg ketamine (95% CIs 0.07/0.22–0.10/0.31 mg/kg), respectively. The hypnotic effects were found to be additive, and there was no evidence of an interaction. At the anesthetic endpoint, the ED₅₀ of ketamine alone was 0.57 mg/kg (95% CIs 0.47–0.69) and the ED₅₀ for ketamine in the presence of midazolam was also 0.57 mg/kg (95% CIs 0.48–0.79); 0.18 mg/kg midazolam was given at this point. Midazolam had no influence on the anesthetic dose of ketamine.

Conclusions: When using the combination, doses employed should be adjusted according to the depth of central nervous system depression that is required. (Key words: Anesthetics, intravenous: ketamine. Hypnotics, benzodiazepines: midazolam. Pharmacology: drug interactions.)

RECENT clinical studies have found combinations of a number of intravenous anesthetic drugs to be syner-

gistic when used for induction of anesthesia. Combinations of midazolam with thiopental, methohexital, propofol, fentanyl, and alfentanil; alfentanil and propofol; and fentanyl and methohexital have been found to be synergistic at endpoints corresponding to hypnosis.^{1–7} Midazolam has also been found to markedly decrease the doses of thiopental, propofol, and alfentanil that are required to suppress movement in response to a noxious stimulus,^{2,4} although midazolam, when given as a sole agent in doses up to 1 mg/kg, was unable to suppress movement in response to a noxious stimulus.²

Midazolam is also commonly combined with ketamine for intravenous induction and maintenance of anesthesia. The combination is favored because midazolam has been shown to attenuate the cardiostimulatory responses of ketamine and to prevent unpleasant emergence reactions.^{8–11} When compared with diazepam, midazolam is superior for the prevention of emergence reactions, and recovery times after anesthesia are shorter.^{10,11} However, dose recommendations for the combination have not taken into account possible sedative interactions,⁹ and the assumption that the sedatives are simply additive has usually been made.⁸ In this study, quantal dose-response curves were determined for the hypnotic and antinociceptive effects of midazolam and ketamine alone and when combined for anesthesia induction.

Materials and Methods

We studied 170 women who presented for minor gynecologic surgery. Criteria for entry into the study were age of 18–40 yr, ASA physical status 1 or 2, weight within 20% of ideal, and no known history of sensitivity to either midazolam or ketamine. Patients who had ingested psychotropic or sedative medication within 1 month of investigation, or who were more than 12 weeks pregnant, were excluded. All patients were unpremedicated. Approval was obtained from the local

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Faculty of Medicine Research Ethics Committee before commencing the study, and informed consent was obtained from all patients.

Three groups of patients were studied. One group received midazolam alone, one group received ketamine alone, and the third group received a combination of ketamine and midazolam. The doses of midazolam used were 0.1, 0.12, 0.14, 0.17, and 0.2 mg/kg, and the doses of ketamine used were 0.4, 0.45, 0.55, 0.7, and 0.85 mg/kg. The range of five midazolam doses used was determined from previous work undertaken by one of the authors, which found the ED_{50} for loss of response to verbal command to be 0.14 mg/kg.⁴ The range of five ketamine doses used was determined from a pilot study of 20 patients, which found the ED_{50} for loss of response to verbal command to be 0.44 mg/kg, and the ED_{50} for suppression of movement to a 5-s electrical tetanus to be 0.74 mg/kg. Doses of the combination were based on a constant ratio between the two ED_{50} s for the endpoint of loss of response to verbal command. The range of doses used for the combination were determined from the results of a further pilot study of 20 patients. They were 0.07/0.22, 0.08/0.25, 0.095/0.3, 0.115/0.36, 0.13/0.41, 0.16/0.5, and 0.19/0.6 mg/kg of midazolam and ketamine, respectively. Patients were randomly allocated to the 17 dosage groups; so that 10 patients received each dose.

Midazolam was made up as a 0.5-mg/ml solution or 1-mg/ml solution, if necessary; and ketamine was made up as a 0.5-mg/ml solution, in 10-ml syringes using physiologic saline as the diluent. After discarding excess drug, the syringe was then filled again to 10 ml, so that all solutions injected were of the same volume and appearance. All injections were made over 10 s into a large forearm vein, and were followed by a 5-ml flush of physiologic saline. The midazolam was given 2 min before the ketamine, and 2 min later a single assessment of depth of sedation was made. The earlier administration of midazolam was necessary because of its slower time to peak sedative effect, as judged by past studies by one of the authors² and the pilot study. At the end of the study period, anesthesia was continued according to standard practice, with more anesthetic induction agent given if clinically indicated.

Two endpoints were assessed. First was the failure to respond to verbal command (*e.g.*, "open your eyes"), which was defined as hypnosis. Second, in those patients who achieved this endpoint, a deeper level of central nervous system depression was assessed. This was movement in response to a noxious stimulus ap-

plied using a 5-s transcutaneous tetanic stimulus (50Hz, 80 mA, 0.25 ms pulses) over the ulnar nerve generated using a constant current peripheral nerve stimulator (Model A-400; Fisher and Paykel, New Zealand). Movement directly caused by the nerve stimulator, stiffening, or hyperventilation were considered a negative response. This noxious stimulus has been found to be equivalent to surgical incision for the determination of minimum alveolar concentration (MAC) for volatile anesthetic agents.¹² The observer was blinded to the doses of each drug given.

Statistical analysis was performed, using ANOVA, to compare age, weight, and height of the patient groups (Statview II; Abacus, Berkeley, CA). For graphic display, the log (dose)-response curves were linearized using probit transformation.¹³ Calculation of the ED_{50} and ED_{95} for hypnosis and anesthesia, for each drug and the combination, was performed by maximum likelihood using the Statistical Package for Social Sciences version 4.0 (SPSS Ltd, Chicago, IL).

Interactions at the hypnotic endpoint were examined by the method of Plummer and Short.¹⁴ It is an extension, to the case of nonparallel 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 nonadditive effects.¹³ When the proportion of patients achieving hypnosis or anesthesia was 0 or 1, the data were excluded from the analysis. Proportions of patients who had achieved hypnosis in each dose group were converted to logits, and the following additive model was fitted to the data by weighted least squares: $Y = \beta_0 + \beta_1 \log(K + (P.M))$, where Y = the logit transformed response; K = the dose of ketamine (mg/kg); M = the dose of midazolam (mg/kg); P = the relative potency at the appropriate effect level; and β_0 and β_1 = variables to be estimated that correspond to the slope and intercept of the log (dose)-response curve. When the dose of midazolam is multiplied by the relative potency, it is converted into the "equivalent" dose of ketamine. Therefore, the term $K + (P.M)$ can be considered as "total ketamine equivalents." Similarly, the term $M + (K/P)$ can be considered as "total midazolam equivalents" (denoted as M_e), and is derived from: $\log(P) = \beta_2 + \beta_3 \log(M_e)$, where $M_e = M + (K/P)$.

The following model, which describes nonadditive behavior, was also fitted to the data: $Y = \beta_0 + \beta_1 \log(K + P.M + \beta_4 (K.P.M.)^{0.5})$, where β_4 relates to that part of the effect observed that cannot be explained on the basis of the effects of the individual drugs; it is analo-

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Table 1. Age, Weight, and Height of Patients in the Three Drug Groups

Group	n	Age (yr)	Weight (kg)	Height (cm)
Midazolam	50	31.9 (5.4)	53.1 (7.7)	155.9 (55)
Ketamine	50	32.9 (5.2)	54.3 (9.6)	153.2 (8.1)
Midazolam + ketamine combination	70	32.0 (6.7)	52.8 (7.2)	156.1 (5.2)

Data are means (with standard deviations in parentheses).
There were no significant differences among the three groups.

gous to Finney's coefficient of synergism, and quantitates the departure from additivity. The combination of drugs was considered to be nonadditive if equation 3 fitted the data significantly better than equation 1. This was done by examining the increase in residual sum of squares after adding the interaction term using an approximate chi-square test. A positive value of β_4 corresponds to synergism, and a negative value implies antagonism.

Interactions at the anesthetic endpoint were analyzed using a different method, because midazolam is not thought to be capable of suppressing movement in response to the noxious stimulus applied when used in the clinically acceptable dose range.² The anesthetic log (dose)-response curve for ketamine was tested for horizontal shift in the presence of midazolam. For this, the proportions of patients anesthetized at each dose were converted to logits, and logistic log (dose)-response curves were fitted by weighted least squares using the Statistical Package for Social Sciences version 4.0. A *P* value of < 0.05 was considered significant.

Results

Demographic data for the three groups of patients are summarized in table 1. Comparisons of age, height, and weight among the three treatment groups revealed no significant differences. The number of patients who were pregnant in each group were: midazolam group, 12; ketamine group, 15; and combination group, 12. There were, again, no significant differences between groups. The proportions of patients that achieved hypnosis and anesthesia in each of the 17 dose categories are listed in table 2. The log (dose)-probit (response) curves for midazolam and ketamine at the hypnotic endpoint are displayed in figure 1. ED₅₀ and ED₉₅ values with 95% confidence intervals are listed in table 3. The

Table 2. Proportions of Patients Achieving Hypnosis and Anesthesia after Each Dose of Midazolam, Ketamine, or the Midazolam + Ketamine Combination

Midazolam (mg/kg)	Ketamine (mg/kg)	Number of Patients	Proportion of Patients	
			Achieving Hypnosis	Achieving Anesthesia
0.1	0	10	0.2	0
0.12	0	10	0.3	0
0.14	0	10	0.7	0
0.17	0	10	0.4	0
0.20	0	10	0.7	0
0	0.4	10	0.6	0.2
0	0.45	10	0.7	0.3
0	0.55	10	0.9	0.5
0	0.7	10	0.9	0.6
0	0.85	10	1.0	0.9
0.07	0.22	10	0.3	0
0.08	0.25	10	0.5	0.2
0.095	0.3	10	0.6	0.1
0.115	0.36	10	0.9	0.1
0.13	0.41	10	0.8	0.1
0.16	0.5	10	1.0	0.4
0.19	0.6	10	1.0	0.6

ED₅₀ of midazolam was 0.15 mg/kg, and the ED₅₀ of ketamine was 0.36 mg/kg. The ED₅₀ for the combination was 0.086/0.27 mg/kg of midazolam and ketamine, respectively. The ED₉₅ of midazolam could not be accurately determined from the data because of the flat dose-response curve and the large amount of extrapolation required.

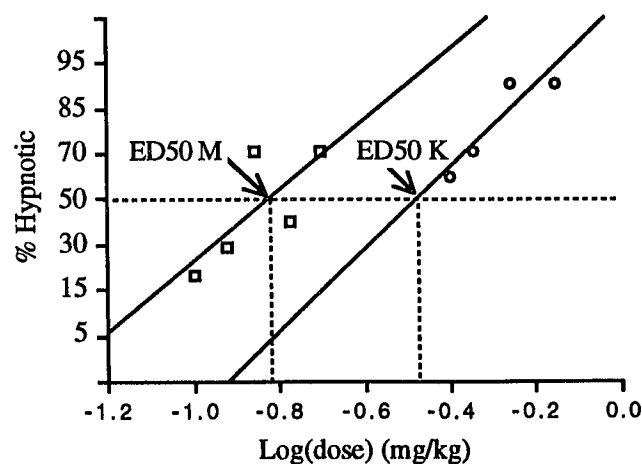


Fig. 1. Log (dose)-probit (response) curves for midazolam (M) and ketamine (K) at the hypnotic endpoint. The ED₅₀ of midazolam was 0.15 mg/kg, and the ED₅₀ of ketamine was 0.36 mg/kg.

Table 3. Calculated ED₅₀ and ED₉₅ for Midazolam, Ketamine, and the Midazolam + Ketamine Combination at Endpoints of Hypnosis and Anesthesia

Drug(s)	ED ₅₀	ED ₉₅
Hypnosis		
Midazolam	0.15 (0.11–0.38)	—
Ketamine	0.36 (0.08–0.44)	0.70 (0.57–3.6)
Midazolam + ketamine combination	0.09/0.27 (0.07/0.22–0.10/0.31)	0.13/0.48 (0.11/0.56–0.20/0.74)
Anesthesia		
Midazolam	—	—
Ketamine	0.57 (0.47–0.69)	1.28 (0.95–2.66)
Midazolam + ketamine combination	0.57/0.18 (0.48–0.79)	1.29/0.41 (0.89–3.3)

ED₅₀ = effective dose for 50% of patients; ED₉₅ = effective dose for 95% of patients.

For hypnosis, the ED₉₅ for midazolam could not be calculated, and anesthesia was not expected; see text. In the data for the midazolam + ketamine combination for anesthesia, confidence intervals are for ketamine only.

The dose-response curve for hypnosis using the midazolam-ketamine combination is compared with the dose-response curves for the individual agents in figure 2. The doses of ketamine and ketamine-midazolam combination have been converted to midazolam equivalents; thus, the ketamine and midazolam dose-response curves lie along the same line. Weighted sums of squares were 8.04 for the additive model and 5.64 for the interaction model ($\beta_4 = -0.35$, $P = 0.14$). The additive model fitted well, and there was no evidence of nonadditivity when using the combination.

The ketamine dose-response curves for anesthesia, when given alone and when given in combination with

midazolam, are presented in figure 3, and the ED₅₀s and ED₉₅s are listed with their 95% confidence intervals in table 3. The ED₅₀ for ketamine alone was 0.57 mg/kg, and the ED₅₀ for ketamine when combined with midazolam was, again, 0.57 mg/kg. The calculated dose of midazolam given at this point on the dose-response curve is 0.18 mg/kg. The addition of midazolam did not significantly alter the slope or position of the anesthesia dose-response curve for ketamine.

Discussion

In the current study, the combination of ketamine and midazolam was found to be additive for the end-

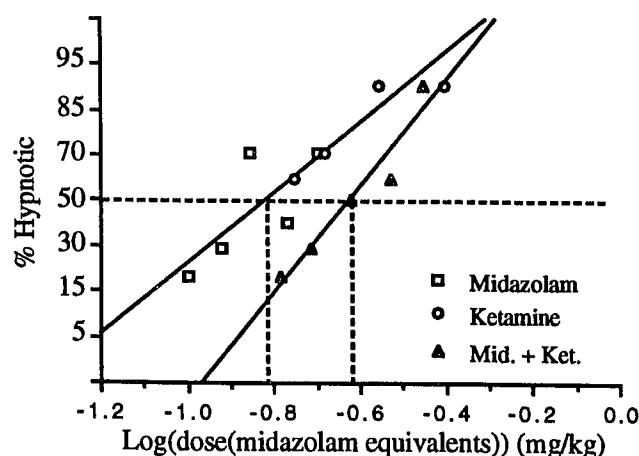


Fig. 2. Log (dose)-probit (response) curves for midazolam, ketamine, and their combination at the hypnotic endpoint. Doses are expressed as midazolam equivalents, and, therefore, the midazolam and ketamine dose-response curves lie on the same line. There was no significant difference between the ED₅₀ of the combination and the ED₅₀ of the individual agents.

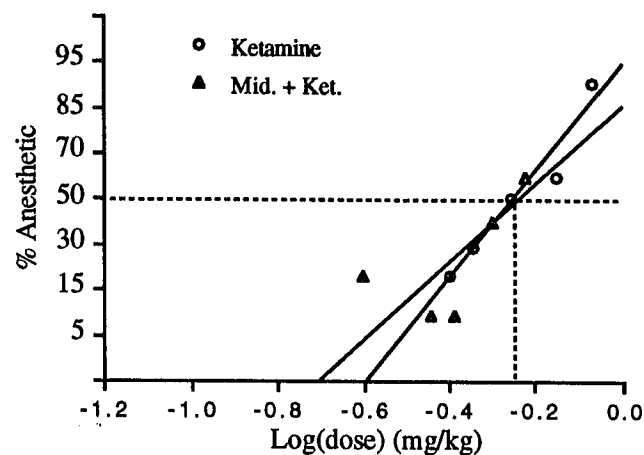


Fig. 3. Log (dose)-probit (response) curves at the anesthetic endpoint for ketamine alone and in combination with midazolam. The ED₅₀ of ketamine was 0.57 mg/kg, and the ED₅₀ of the ketamine-midazolam combination was 0.57/0.18 mg/kg of ketamine and midazolam, respectively.

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point of loss of response to verbal command. Midazolam was found to have no influence on the dose of ketamine required to suppress movement in response to a 5-s tetanus. At the hypnotic endpoint, the finding is in contrast to similar studies in humans of midazolam combined with other intravenous anesthetic induction agents, such as thiopental, methohexital, propofol, fentanyl, and alfentanil,¹⁻⁷ in which synergism in their combined actions has been repeated. Additivity has, however, been previously found in a study of thiopental and ketamine interactions at a hypnotic endpoint,¹⁵ and in a study of midazolam and morphine at an endpoint of light sedation.¹⁶ At the anesthetic endpoint, it is also in contrast to similar studies in humans in which midazolam has also been found to be synergistic with thiopental, propofol, and alfentanil,^{2,4} but similar to a study of thiopental and ketamine in which additivity was found at an endpoint of failure to respond to noxious pressure applied to the trapezius muscle.¹⁵

The reason that the drugs are not synergistic may relate to the postulated mechanism of action of ketamine, which is distinct from that postulated for midazolam and other intravenous induction agents that demonstrated synergism with midazolam. Ketamine acts at N-methyl D-aspartate (NMDA) receptors, which mediate synaptic excitation in the central nervous system *via* regulation of calcium ion influx. Ketamine antagonizes NMDA receptor responses by binding inside the ligand-gated receptor channel complex and, hence, blocking calcium influx.¹⁷ The antagonism is noncompetitive, use dependent (the receptor must first be activated by an agonist), and voltage dependent.¹⁸⁻²⁰

Midazolam acts at specific benzodiazepine receptors in the central nervous system. These receptors are closely associated with receptor sites for γ -amino butyric acid (GABA) at the GABA_A receptor in the form of an ionophore complex. GABA is an inhibitory neurotransmitter, and receptor occupancy by a benzodiazepine agonist causes an increase in the affinity of GABA for its receptor. This leads to GABA-mediated potentiation of inward chloride conductance with subsequent membrane hyperpolarization and, hence, neuronal inhibition.²¹ Thiopental is also thought to have sedative actions at the GABA_A receptor,^{21,22} and opioids such as alfentanil, which act at opiate receptors, are thought to have functional links to the GABA_A receptor.⁶ Although ketamine has also been postulated to have analgesic actions at opiate receptors,²³ the evidence in humans has not been confirmed,²⁴ and the theory remains controversial.²⁵ The contrasting modes of action

of ketamine and midazolam, which are thought to act at different central nervous system receptors, and the use-dependent nature of ketamine effects, indicate that a sedative such as midazolam would not be expected to potentiate ketamine actions, and, indeed, may be more likely to antagonize them.

Using ketamine as a sole agent, the ED₅₀ for hypnosis of 0.36 mg/kg in the current study was similar to that found by Stella *et al.* of 0.40 mg/kg using similar methodology,²⁶ but substantially less than the ED₅₀ of 0.76 mg/kg found by Roytblatt *et al.*¹⁵ and 0.9 mg/kg found by Gross *et al.*²⁷ Our ED₅₀ value of 0.57 mg/kg for anesthesia using ketamine was similar to the ED₅₀ of 0.64 mg/kg found by Roytblatt *et al.* using an endpoint of noxious pressure on the trapezius muscle, but, again, was substantially less than the ED₅₀ of 1.3 mg/kg found by Gross *et al.*²⁷ Our ED₉₅ value of 1.28 mg/kg for anesthesia using ketamine was in line with current dose recommendations of 1–2 mg/kg for ketamine as an induction agent.⁹ Use of an incremental dose regimen, and differences in interpretation of involuntary movements associated with ketamine administration, probably account for the large difference in dose requirements found in the study by Gross *et al.* The ED₅₀ of ketamine for hypnosis in the current study was also estimated with less precision than is desirable, because the range of doses chosen were high in relation to the ED₅₀ at this endpoint. This imprecision is reflected in the wide confidence intervals for this value, and it is also taken into account by the analysis used for the interaction model. The validity of the result also rests on the assumption that the log (dose)-probit (response) curves are linear. The ED₅₀ of 0.15 mg/kg for midazolam for hypnosis was similar to that in past studies, which have found it to be between 0.14 and 0.19 mg/kg.^{1-5,27} Unfortunately, it was not possible to confirm the cardiovascular stability of the midazolam-ketamine combination using our study format, because of the short observation period, multiple doses used, and varying stimuli applied depending on the depth of sedation observed.

We found the combination of midazolam and ketamine for anesthesia induction to be additive at an endpoint of loss of response to verbal command, and we found midazolam to have no influence on the dose of ketamine required to suppress movement in response to a 5-s electrical tetanus. When using the combination, doses employed should be adjusted accordingly, depending on the depth of central nervous system depression required. The combined effects of the drugs

were also different at different levels of central nervous system depression, and this supports the proposal that, when combinations of intravenous anesthetic drugs are given for anesthesia induction, the combination should be regarded as a new "drug" with unique properties,⁴ rather than as simply reflecting the properties of the individual drugs given.

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