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Additive Interactions between Propofol and Ketamine When Used for Anesthesia Induction in Female Patients

T. W. Hui, M.B., B.S., T. G. Short, M.D.,† W. Hong, M.B., B.S.,* T. Suen, M.B., B.S.,* T. Gin, M.D.,‡ J. Plummer, Ph.D.§*

Background: **Propofol and ketamine may be paired for anesthesia induction and for total intravenous anesthesia. The nature of any sedative interactions occurring between propofol and ketamine are unknown. The combination when used for anesthesia induction in female patients was studied.**

Methods: **Quantal dose-response curves were determined in 180 female patients to whom the drugs were administered individually and in combination. Two minutes after administering the drugs, two endpoints were assessed. First, loss of response to verbal command (hypnosis) and then, in those who failed to respond to this endpoint, loss of response to a 5-s transcutaneous tetanus (anesthesia). Interactions were analyzed by fitting the data to a mathematical model in which response was analyzed in terms of the doses of the two drugs and an additional term included to describe nonadditive interactions. The incidences of apnea, arterial pressure, and heart rate changes during the first 5 min were recorded.**

Results: **At the hypnotic endpoint, the ED_{50}s were 1.10 mg/kg propofol (95% CIs 0.93–1.27), 0.39 mg/kg ketamine (95% CIs 0.27–0.46), and the combination of 0.63 mg/kg propofol and 0.21 mg/kg ketamine (95% CIs 0.53/0.18–0.73/0.24). At the anesthetic endpoint, the ED_{50}s were 1.85 mg/kg propofol (95% CIs 1.58–2.36), 0.66 mg/kg ketamine (95% CIs 0.58–0.77), and the combination of 1.05 mg/kg propofol and 0.35 mg/kg ketamine (95% CIs 0.88/0.29–1.27/0.42). The effects were additive at both endpoints; there was no evidence of an interaction. The ED_{50}s for apnea were 1.61 mg/kg propofol (95% CIs 1.39–1.94), greater than 0.85 mg/kg ketamine and for the combination 1.50 mg/kg propofol and 0.50 mg/kg ketamine (95% CIs 1.15/0.38–3.09/1.03). The addition of ketamine did not significantly alter the ED_{50} for apnea of propofol. There was a significant difference in the arterial pressures among the three groups ($P < 0.001$). Using the combination, the cardiostimulant effects of ketamine balanced the cardiodepressant effects of propofol. There was no change in arterial pressure or heart rate after the noxious stimulus.**

Conclusions: **When using the combination, doses were additive at hypnotic and anesthetic endpoints. Ketamine had no influence on the incidence of apnea after propofol, and the net hemodynamic effects were minimal. (Key words: Anesthetics, intravenous: ketamine; propofol. Pharmacology drug interactions.)**

WHEN combinations of intravenous anesthetic agents are given to patients, the degree of sedation that results cannot be predicted from a knowledge of the dose requirements and sedative effects of the individual agents.[1,2] Past studies using loss of response to verbal command as an endpoint for anesthesia induction have found combinations of midazolam with thiopental,[3,4] methohexital,[5] propofol,[1] alfentanil,[1,6] and fentanyl[7] to be synergistic. Midazolam also decreased the doses of thiopental,[4] propofol,[1] and alfentanil[1] required to suppress movement in response to a noxious stimulus. In contrast, ketamine has been found to be additive when combined with midazolam[2] or thiopental[8] using loss of response to verbal command as the endpoint. The dose of ketamine required to suppress movement in response to a noxious stimulus was also additive with thiopental[8] but not altered by the presence of midazolam.[2]

The combination of ketamine and propofol has been used for total intravenous anesthesia.[9–11] Advantages of using the combination have included hemodynamic stability intraoperatively and, when compared with the use of propofol and fentanyl in combination, superior analgesia with less respiratory depression during the

* Medical Officer, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong.

† Senior Lecturer, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong.

‡ Reader, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong.

§ Principal Hospital Scientist, Flinders Medical Centre, Adelaide, Australia.

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Address reprint requests to Dr. Short: Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong.

early recovery phase. No unpleasant emergence phenomena were reported when using the combination.

In this study, we examined the interactions that occur when ketamine and propofol are combined at anesthesia induction. Interactions were assessed at endpoints of loss of response to verbal command and loss of response to a noxious stimulus. The incidence of apnea and the arterial pressure and heart rate changes also were recorded.

Patients and Methods

After obtaining approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong Faculty of Medicine, we performed a prospective study with 180 female patients who presented for minor gynecologic surgery. Criteria for entry into the study were age 18–40 yr, ASA physical status 1 or 2, weight within 20% of ideal, and no known contraindication to the use of propofol or ketamine. Patients who had ingested psychotropic or sedative medication within 1 month of investigation, who were undergoing termination of pregnancy, or who were more than 10 weeks pregnant were excluded. All patients were unpremedicated. Informed consent for the study was obtained from all patients.

Patients were randomly allocated to one of three treatment groups. One group received propofol alone, one group ketamine alone, and the third group propofol and ketamine in combination. The range of doses used, dose ratio for the combination, and timing of assessments were based on previous research by the authors.[1,2] Half the hypnotic ED_{50} of propofol was combined with half the hypnotic ED_{50} for ketamine. A range of doses about these ED_{50}s was chosen, maintaining a constant dose ratio between the two drugs. The doses of propofol given were 0.8, 1.0, 1.2, 1.5, 1.9, and 2.4 mg/kg; the doses of ketamine given were 0.32, 0.39, 0.47, 0.58, 0.70, and 0.85 mg/kg; and the doses of propofol and ketamine in combination given were 0.45/0.15, 0.6/0.2, 0.78/0.26, 1.05/0.35, 1.38/0.46, and 1.8/0.6 mg/kg, respectively. Ten patients received each dose. All drugs were injected over 10 s into a peripheral vein and followed by a flush of 5 ml physiologic saline. In the case of only one drug being administered, physiologic saline was used in the second syringe. The patient and observer were blind to the doses and drugs administered.

Patients were assessed for hypnosis and anesthesia 2 min after the injections, these being the approximate time to peak effect for the two drugs when given in intravenous boluses.[1,2] Hypnosis was assessed using failure to open the eyes on verbal command as the criterion. In those patients who achieved hypnosis, anesthesia was then assessed using failure to move in response to a 5-s transcutaneous tetanic stimulus (50 Hz, 80 mA, 0.25 ms pulses) applied over the ulnar nerve in the forearm using a constant current peripheral nerve stimulator (Model A-400, Fisher and Paykel, Auckland, New Zealand). Movement directly caused by the nerve stimulator in the stimulated arm, stiffening, or hyperventilation was considered a negative response. A similar electrical stimulus has been found to be similar in intensity to surgical incision for the determination of minimum alveolar concentration (MAC) for volatile anesthetic agents.[12] To standardize the verbal command and assessments of response, all observers for the study attended a series of training sessions before commencement of the study. After the end of the study period, anesthesia continued according to standard practice with more intravenous anesthetic induction agent given as indicated. Patients also were assessed for apnea, which was defined as loss of respiratory effort for 20 s or longer. Arterial pressure and heart rate were recorded at 1-min intervals using an automated oscillometric arterial pressure recorder (Dinamap 1846SX, Critikon, Tampa, FL). Measurements were commenced before induction and continued for 5 min after injection of the drug(s). Oxygen saturation and electrocardiogram also were monitored in accordance with standard practice.

Statistical analysis was performed using analysis of variance to compare the age, weight, and height of patients in the three groups (Statview II, Abacus, Berkeley, CA). For graphics display, the log(dose)-response curves were linearized using probit transformation.[13] Calculation of the ED_{50}s and ED_{95}s 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). Simulations of the predicted plasma concentrations at the time of assessment were made using published pharmacokinetic data for propofol[14] and ketamine.[15]

Interactions at the hypnotic and anesthetic endpoints were examined by the method of Plummer and Short.[16] 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 hypothesis of additive effects and nonadditive ef-

fects.[13] When the proportion of patients achieving hypnosis or anesthesia was 0 or 1.0, 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:

$$Y = \beta_0 + \beta_1 \log (K + (R \cdot P)), \quad (1)$$

where Y is the logit transformed response; K is the dose of ketamine (mg/kg); P is the dose of propofol (mg/kg), R is the relative potency at the appropriate effect level; and β_0 and β_1 are parameters to be estimated that correspond to the slope and intercept of the log(dose)—response curve. When the dose of propofol is multiplied by the relative potency, it is converted into the "equivalent" dose of ketamine. Therefore the term $K + (R \cdot P)$ can be considered as "total ketamine equivalents." Similarly, the term $P + (K/R)$ can be considered as "total propofol equivalents" (denoted as Pe) and is derived from:

$$\log (R) = \beta_2 + \beta_3 \log (Pe), \quad (2)$$

where $Pe = P + (K/R)$.

The following model, which describes nonadditive behavior, was also fitted to the data:

$$Y = \log (K + R \cdot P + \beta_4 (K \cdot R \cdot P)^{0.5}), \quad (3)$$

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 analogous to Finney's coefficient of synergism. 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, whereas a negative value implies antagonism.

Mean arterial pressure and heart rate changes were compared by analysis of variance for repeated measures using the factors group, dose, and degree of sedation. This was performed initially including all patients in each group and then repeated for two subsets of patients: those for whom the hypnotic endpoint but not the anesthetic endpoint was achieved and those for whom the anesthetic endpoint was achieved. In patients for whom the anesthetic endpoint was achieved, mean arterial pressure and heart rate immediately before the tetanic stimulus also were compared with values following the stimulus.

Results

Demographic data for patients in the three treatment groups are summarized in table 1. Comparisons of age, weight, and height among the three treatment groups revealed no significant differences. The number of patients who were undergoing dilatation and curettage for recent miscarriage in each group were propofol group 21, ketamine group 16, and combination group 18; there was no significant difference between groups. The proportions of patients for whom hypnosis, anesthesia, and apnea were achieved in each of the 18 dose categories are listed in table 2, and the ED_{50}s and ED_{95}s for hypnosis, anesthesia, and apnea for the three groups are listed in table 3.

For the propofol group, the ED_{50}s were 1.10 mg/kg for hypnosis and 1.85 mg/kg for anesthesia (fig. 1). For the ketamine group, the ED_{50}s were 0.39 mg/kg for hypnosis and 0.66 mg/kg for anesthesia (fig. 2). For the combination, the ED_{50}s were 0.63 mg/kg propofol and 0.21 mg/kg ketamine for hypnosis and 1.05 mg/kg propofol and 0.35 mg/kg ketamine for anesthesia. The ED_{50} for apnea using propofol was 1.61 mg/kg. Ketamine only caused apnea in two patients in the doses used, and no ED_{50} could be calculated. Using the combination, the ED_{50} was 1.50 mg/kg propofol and 0.50 mg/kg ketamine. Ketamine had no influence on the dose of propofol required to cause apnea.

Simulations of the arterial concentrations for the ED_{50} (ED_{95}) doses of propofol and ketamine at the time of assessment gave the following estimates: hypnotic endpoint, ketamine 0.6 (1.2) μg/ml, propofol 2.4 (4.2) μg/ml, and propofol and ketamine combination 0.3 (0.5) μg/ml and 1.4 (2.5) μg/ml, respectively; anesthesia endpoint, ketamine 1.0 (1.6) μg/ml, propofol 4.0 (7.8) μg/ml, and propofol and ketamine combination 0.5 (1.0) μg/ml and 2.9 (4.3) μg/ml, respectively; and apnea, propofol alone 3.5 (6.5) μg/ml and combined with ketamine 3.3 μg/ml.

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

Group	n	Age (yr)	Weight (kg)	Height (cm)
Propofol	60	33.6 ± 5.1	56 ± 8	157 ± 5
Ketamine	60	33.1 ± 5.7	54 ± 8	156 ± 4
Propofol + ketamine	60	32.8 ± 5.0	53 ± 9	157 ± 5

Data are mean ± SD. There were no significant differences among the three groups.

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

Propofol (mg/kg)	Ketamine (mg/kg)	No. of Patients	Achieving Hypnosis	Achieving Anesthesia	Becoming Apneic
0.8	0	10	0.3	0.1	0
1.0	0	10	0.2	0	0.2
1.2	0	10	0.6	0.2	0.2
1.5	0	10	0.8	0.1	0.3
1.9	0	10	1.0	0.6	0.7
2.4	0	10	1.0	0.8	0.9
0	0.32	10	0.2	0	0
0	0.39	10	0.7	0	0
0	0.47	10	0.6	0.2	0
0	0.58	10	0.9	0.4	0.1
0	0.7	10	0.9	0.4	0
0	0.85	10	0.9	0.9	0.1
0.45	0.15	10	0.1	0	0
0.6	0.2	10	0.4	0	0.1
0.78	0.26	10	0.9	0.2	0.1
1.05	0.35	10	0.9	0.4	0.3
1.38	0.46	10	1.0	0.8	0.4
1.8	0.6	10	1.0	0.9	0.6

The dose-response curves for hypnosis using the ketamine-propofol combination are compared with the dose-response curves for the individual agents in figure 3. In this graph, the doses of ketamine and the ketamine component of the combination have been converted to propofol equivalents so that the propofol and ketamine dose-response curves lie along the same line.

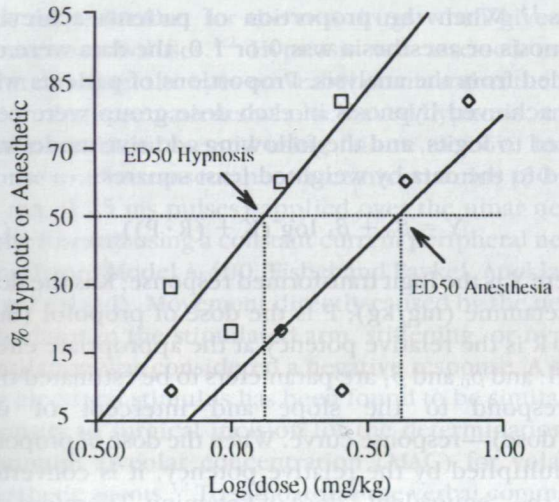

Fig. 1. Log(dose)-probit(response) curves for propofol at the hypnotic and anesthetic endpoints. The ED_{50}s of propofol were 1.10 mg/kg for hypnosis and 1.85 mg/kg for anesthesia.

Weighted sums of squares were 8.34 for the additive model and 7.74 for the nonadditive model ($\beta_4 = -0.20$, $P > 0.45$). Therefore, there was no evidence of a nonadditive interaction when using this combination, and the additive model was chosen to describe the interaction. Similar dose-response curves for the anesthetic endpoint are graphed in figure 4. Weighted sums of squares for the additive model were 6.99 and for the nonadditive model 5.53 ($\beta_4 = -0.24$, $P > 0.2$); again the additive model was chosen to describe the interaction.

Table 3. Calculated ED_{50} and ED_{95} for Propofol, Ketamine, and the Propofol + Ketamine Combination at End Points of Hypnosis, Anesthesia, and Apnea

Drug(s)	ED_{50}	ED_{95}
Hypnosis		
Propofol	1.10 (0.93–1.27)	1.93 (1.57–3.36)
Ketamine	0.39 (0.27–0.46)	0.84 (0.64–2.21)
Propofol + ketamine	0.63/0.21 (0.53/0.18–0.73/0.24)	0.97/0.33 (0.83/0.28–1.71/0.57)
Anesthesia		
Propofol	1.85 (1.58–2.36)	3.62 (2.68–9.02)
Ketamine	0.66 (0.58–0.77)	1.07 (0.87–1.93)
Propofol + ketamine	1.05/0.35 (0.88/0.29–1.27/0.42)	2.02/0.67 (1.56/0.52–3.82/1.27)
Apnea		
Propofol	1.61 (1.39–1.94)	3.02 (2.34–5.95)
Ketamine	—	—
Propofol + ketamine	1.50/0.50 (1.15/0.38–3.09/1.03)	—

Values in parentheses are 95% confidence intervals.

ED_{50} = effective dose for 50% of patients; ED_{95} = effective dose for 95% of patients. For apnea the ED_{50} and ED_{95} for ketamine and ED_{95} for the combination could not be calculated.

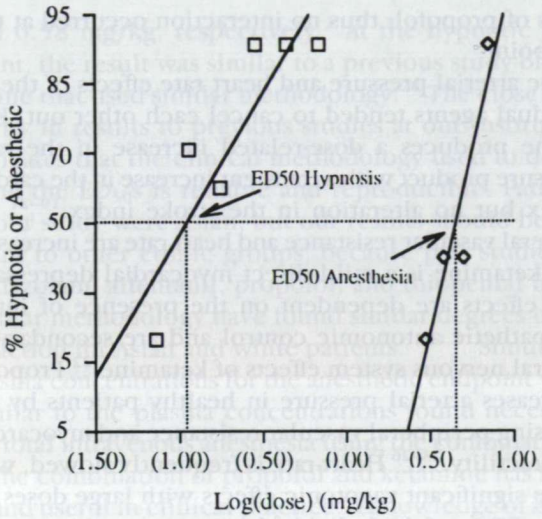

Fig. 2. Log(dose)-probit(response) curves for ketamine at the hypnotic and anesthetic endpoints. The ED_{50}s of ketamine were 0.39 mg/kg for hypnosis and 0.66 mg/kg for anesthesia.

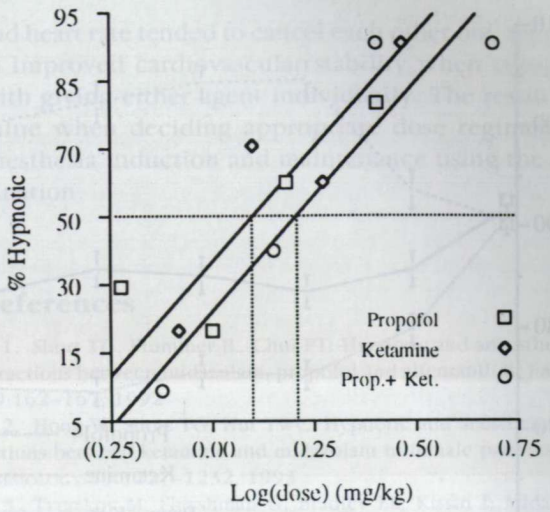

Fig. 3. Log(dose)-probit(response) curves for propofol, ketamine, and their combination at the hypnotic endpoint. Doses are expressed as propofol equivalents, and therefore, the ketamine and propofol dose response curves lie on the same line (*left*). There was no significant difference between the ED_{50} of the combination and the ED_{50}s of the individual agents.

Changes in mean arterial pressure and heart rate over the 5-min period of observation are graphed in figures 5 and 6. There were significant between group, time, and group × time differences among the three groups in both variables ($P < 0.001$). In the propofol group, mean arterial pressure and heart rate decreased, to a maximum of −17 mmHg and −8 beats/min, respectively. In the ketamine group, mean arterial pressure and heart rate increased, by a maximum 14 mmHg and 14 beats/min, respectively. Using the combination, there was a small yet significant decrease in arterial pressure—the maximum change was −8 mmHg—and heart rate did not change significantly. The net effect of the combination was to cancel out the cardiostimulant effects of ketamine and the cardiodepressant effects of propofol. The arterial pressure and heart rate effects were not found to be dependent on either dose or degree of sedation observed in the dose range used. No significant pressor effects were recorded in those patients who received the noxious stimulus.

Discussion

The sedative effects of the combination of ketamine and propofol were found to be additive at endpoints of hypnosis and anesthesia. The result is similar to the additivity previously found using combinations of ketamine and midazolam[2] or thiopental[8] at the endpoint of hypnosis and ketamine and thiopental[8] at the endpoint of anesthesia.

Synergism has been found between agents with known functional links in the central nervous system.[1,6]

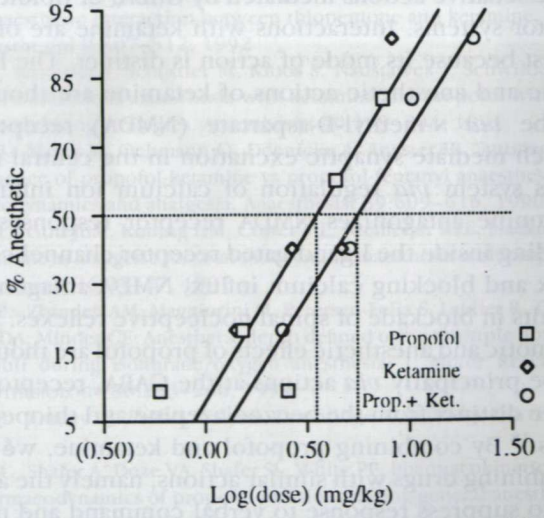

Fig. 4. Log(dose)-probit(response) curves for propofol, ketamine, and their combination at the anesthetic endpoint. Doses are expressed as propofol equivalents, and therefore, the ketamine and propofol dose response curves lie on the same line (*left*). There was no significant difference between the ED_{50} of the combination and the ED_{50}s of the individual agents.

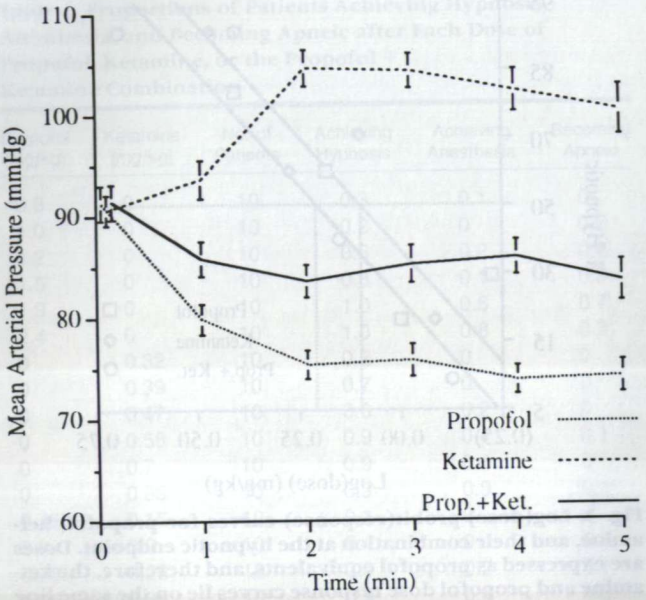

Fig. 5. Change in mean arterial pressure over the 5 min after administration of propofol, ketamine, and their combination. There were significant group, time, and group × time differences for all three groups ($P < 0.001$). Error bars are SEM.

Examples are combinations of benzodiazepines with thiopental, propofol, and opioids and combinations of opioids with thiopental or propofol. These drugs all have sedative actions mediated by $GABA_A$ or opioid receptor systems. Interactions with ketamine are of interest because its mode of action is distinct. The hypnotic and anesthetic actions of ketamine are thought to be *via* N-methyl-D-aspartate (NMDA) receptors, which mediate synaptic excitation in the central nervous system *via* regulation of calcium ion influx.[17] Ketamine antagonizes NMDA receptor responses by binding inside the ligand-gated receptor channel complex and blocking calcium influx. NMDA antagonism results in blockade of spinal nociceptive reflexes. The hypnotic and anesthetic effects of propofol are thought to be principally *via* actions at the $GABA_A$ receptor at a site distinct from the benzodiazepine and thiopental sites.[18] By combining propofol and ketamine, we are combining drugs with similar actions, namely the ability to suppress response to verbal command and noxious stimuli, but where their postulated modes of action are distinctly different. In this instance, simple additivity resulted even though their modes of action are different. Ketamine, which did not cause apnea in the dose range used, also did not influence the apneic effects of propofol; thus no interaction occurred at this endpoint.

The arterial pressure and heart rate effects of the individual agents tended to cancel each other out. Ketamine produces a dose-related increase in the rate-pressure product with a transient increase in the cardiac index but no alteration in the stroke index.[19–21] Peripheral vascular resistance and heart rate are increased, and ketamine is a mild direct myocardial depressant. The effects are dependent on the presence of intact sympathetic autonomic control and are secondary to central nervous system effects of ketamine.[22] Propofol decreases arterial pressure in healthy patients by decreasing peripheral vascular resistance and myocardial contractility.[23–26] Heart rate is frequently slowed, with more significant vagotonic effects with large doses.

The ED_{50}s of the individual agents were close to previous values found in our institution. In a similar dose-finding study for propofol, we found the ED_{50}s for hypnosis and anesthesia to be 1.04 mg/kg and 1.97 mg/kg, respectively,[1] and another study using similar methodology found the ED_{50} of propofol for loss of response to verbal command to be 1.11 mg/kg.[27] For ketamine, a previous study in our institution found the ED_{50}s for hypnosis and anesthesia to be 0.36 mg/kg

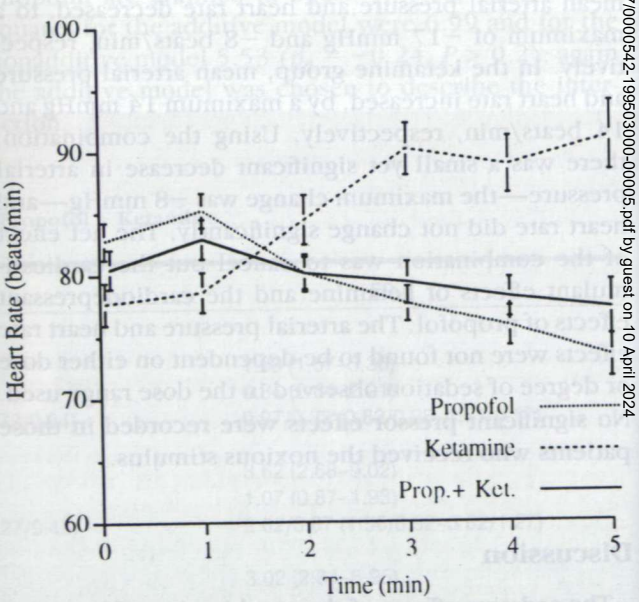

Fig. 6. Change in heart rate over the 5 min after administration of propofol, ketamine, and their combination. There were significant group, time, and group × time differences for all three groups ($P < 0.001$), except that heart rate did not change significantly over time using the combination. Error bars are SEM.

and 0.58 mg/kg, respectively.[2] At the hypnotic endpoint, the result was similar to a previous study of ketamine that used similar methodology.[28] The close similarity in results to previous studies at our institution indicates that the clinical methodology used to determine the ED_{50}s is reliable and reproducible. Patients in our study were Asian, but our results should be relevant to other ethnic groups, because past studies of midazolam, alfentanil, propofol, and thiopental using similar methodology have found similar degrees of interaction for Asian and white patients.[1,3,4,27] Simulated plasma concentrations for the anesthetic endpoint were similar to the plasma concentrations found necessary for total intravenous anesthesia using the combination.[9]

The combination of propofol and ketamine has been found useful in clinical practice. A knowledge of ED_{50}s and ED_{95}s for the combination is useful when deciding appropriate dose regimens for the combination, particularly when used for intravenous induction of anesthesia. However, we have tested the degree of interaction using the combination at only one dose ratio; the degree of interaction between the drugs at other dose ratios may be different. We also have tested the interactions only during induction of anesthesia; therefore, caution must be exercised in extrapolating the result to dose recommendations for infusions of the two drugs for intravenous maintenance of anesthesia.

In the current study, the 5-s tetanic stimulation was not followed by a vasopressor response or increase in heart rate. A previous study of isoflurane found vasopressor response after a 10-s tetanus stimulation to be less than half the vasopressor response of surgical incision, whereas the difference in motor responses with the two different noxious stimuli were insignificant.[12,29] Thus, use of tetanic stimulus as a noxious stimulus does not accurately reflect the hemodynamic responses to incision. This is probably because of the brief period of stimulation when compared with the continuous nature of pain due to surgical incision. The period of observation after application of the noxious stimulus in the current study also may have been too brief to detect the maximum vasopressor response.

In summary, we have found the sedative effects of ketamine and propofol to be additive at endpoints of hypnosis and anesthesia. Ketamine had no influence on the incidence of apnea after propofol, which means that one can achieve the hypnotic or anesthetic endpoint with a lower probability of apnea. The opposing effects of ketamine and propofol on arterial pressure and heart rate tended to cancel each other out, resulting in improved cardiovascular stability when compared with giving either agent individually. The result is of value when deciding appropriate dose regimens for anesthesia induction and maintenance using the combination.

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