

## Respiratory Interactions of Ketamine and Morphine

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Six healthy, consenting volunteer males received ketamine iv in five logarithmically scaled doses totaling 3 mg/kg on three occasions each. The sessions differed only in the initial injection of an unknown drug: placebo, morphine sulfate 0.2 mg/kg, or morphine sulfate 0.4 mg/kg. Initial and terminal steady-state ventilatory responses to CO<sub>2</sub> ( $\dot{V}_E R_{CO_2}$ ) and isohypercapnic ventilation (end-tidal CO<sub>2</sub> 49.8 ± 2.4 mmHg) during drug administration assessed CO<sub>2</sub>-mediated ventilatory drive. Oxygen concentration of 40% ablated hypoxic drive contribution. Morphine caused a decrease of isohypercapnic ventilation ( $\dot{V}_E$ ) of 8.2 ± 1.2 l/min after 0.2 mg/kg. Doubling the dose to 0.4 mg/kg gave a further depression of 6.6 ± 1.8 l/min. No subject lost consciousness after morphine. Over a dose range of 0.39 to 3.0 mg/kg ketamine caused log-linear dose-related depression of 1.6 ± 0.3 l/min for each doubling of dose, although the first significant depression of 4.9 ± 1.1 l/min did not occur until the third dose (1.1 mg/kg) in the absence of morphine. All subjects were unconscious after 1.8 mg/kg ketamine. Slopes of the  $\dot{V}_E R_{CO_2}$  did not differ from control, regardless of the pretreatment, placebo, or morphine in the two doses. Ketamine alone, 3.0 mg/kg, caused a displacement of  $\dot{V}_E R_{CO_2}$  of +2.0 ± 1.2 mmHg in CO<sub>2</sub>, while combination of ketamine and morphine in either dose caused a +10 mmHg displacement of  $\dot{V}_E R_{CO_2}$ . Thus, ketamine appears qualitatively similar but less potent than premedicant doses of morphine in depressing respiration despite near equipotency in producing loss of consciousness. (Key words: Analgesics: ketamine; morphine. Anesthetics, intravenous: ketamine; morphine. Carbon dioxide: ventilatory response. Interactions: drug. Ventilation: control.)

KETAMINE HAS BEEN in general use since 1970. Initial enthusiasm for the drug has waned with confirmation of several undesirable side effects, including notably unpleasant emergence reactions<sup>1,2</sup> and hypertension from cardiovascular stimulation.<sup>3,4</sup> Despite these problems, useful indications for ketamine have emerged. Among others, it has been used for burn patients undergoing debridement and grafting and as an adjunct to regional anesthesia, a postoperative analgesic, and an induction agent for asthmatic or hypovolemic patients.<sup>5-8</sup>

Ketamine's influence on respiration, however, is an aspect of the drug's pharmacology that has received little

attention, and available reports are either equivocal or contradictory. Its effects that have been reported are nil,<sup>9</sup> depressant,<sup>10,11</sup> and stimulant.<sup>12,13</sup> The methodology that led to these conclusions does not permit unequivocal analysis of the action of ketamine on CO<sub>2</sub>-mediated respiratory control. This study was designed to examine the effects on respiratory control caused by ketamine alone and ketamine after pretreatment with morphine using both steady-state CO<sub>2</sub> response curves and the isohypercapnic ventilatory response. Our results in human volunteers, using the steady-state ventilatory response to CO<sub>2</sub> and the isohypercapnic technique of Lambertson and Wendel,<sup>14</sup> indicate that ketamine is a respiratory depressant similar to but less potent than morphine.

### Methods

We studied six healthy adult informed and consenting male volunteers aged 18-30 yr, each on three separate occasions separated by at least 1 week, and our protocol was approved by institutional review. Subjects refrained from using drugs and fasted for 8 h before each study session. After ECG electrodes and a blood pressure cuff were applied and an intravenous infusion of normal saline started, semirecumbent subjects breathed through a high-flow-low-resistance breathing circuit previously described<sup>15</sup> for a 10-min acclimatization period. After determining the ventilatory response to CO<sub>2</sub> challenge at 0%, 3%, 5%, and 7% CO<sub>2</sub>, we lowered inspired CO<sub>2</sub> (F<sub>I</sub>CO<sub>2</sub>) to 5%. The end-tidal CO<sub>2</sub> (PETCO<sub>2</sub>) observed at the end of 5 min of breathing 5% CO<sub>2</sub> was maintained throughout the next, isohypercapnic, phase by varying the F<sub>I</sub>CO<sub>2</sub>. For each study session, when the PETCO<sub>2</sub> stabilized, each subject received an unknown intravenous injection, either placebo or morphine sulfate, 0.2 mg/kg, or 0.4 mg/kg of body weight. Fifteen minutes after the injection, we began a series of 5 iv injections of ketamine spaced at 10-min intervals. The individual doses in mg/kg of body weight were: 1) 0.39; 2) 0.26; 3) 0.43; 4) 0.72; and 5) 1.20. This dose sequence yields a logarithmic progression of cumulative dose, with the total dose being 3.0 mg/kg (*i.e.*, 0.39, 0.65, 1.08, 1.80, and 3.00 mg/kg, respectively). During the eighth to tenth minute after each ketamine injection, we measured minute ventilation ( $\dot{V}_E$ ), F<sub>I</sub>CO<sub>2</sub>, mixed expired CO<sub>2</sub>, and PETCO<sub>2</sub>. After the final observations, a change in F<sub>I</sub>CO<sub>2</sub> sufficient to cause a 6-8 mmHg change in PETCO<sub>2</sub> was maintained for 8 min, permitting determination of a second CO<sub>2</sub> response curve. One hour after the last ketamine injection subjects were challenged with two levels of inspired CO<sub>2</sub> and a

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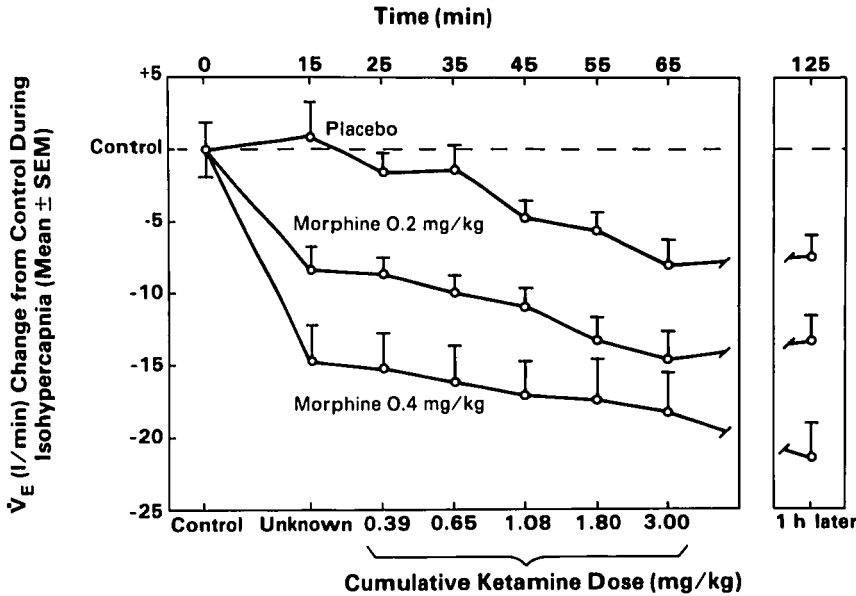


FIG. 1. Isohypercapnic minute ventilation ( $\dot{V}_E$  l/min, mean  $\pm$  SEM) shown as change from control value with end-tidal  $\text{CO}_2$  controlled at  $49.8 \pm 2.4$  mmHg (mean  $\pm$  SD),  $6.1 \pm 0.3$  mmHg above control. Control  $\dot{V}_E$  was  $23.2 \pm 1.8$  l/min (mean  $\pm$  SD). One-hour values were interpolated from  $\text{CO}_2$  response curves. Both doses of morphine caused a significant decrease in  $\dot{V}_E$ . In all three cases the slope of  $\dot{V}_E$  vs. ketamine was significantly different from zero.

final  $\text{CO}_2$  response curve was determined. Inspired oxygen concentration was maintained near 40% during respiratory measurements. Respiratory minute volume was calculated at BTPS.

Statistical analysis included analysis of variance, Student's *t* test (Dunnett's Method for Multiple Comparisons with a Control), and linear regression analysis.  $P < 0.05$  was considered significant.<sup>16</sup> Statistical power estimates for all comparisons ranged from 0.80 to 0.95.<sup>17</sup> All results are reported as mean  $\pm$  SEM unless otherwise noted.

## Results

### GENERAL

Six subjects completed all three sessions. They related subjective reactions that varied from quite pleasant to mildly unpleasant, regardless of regimen. A seventh subject withdrew after his first session (placebo-ketamine) due to an unpleasant emergence reaction.<sup>18</sup>

Throughout the 19 study sessions there were no changes in blood pressure (BP) or heart rate (HR) greater than 25% of control. No abnormal electrocardiographic events were recorded. Neither the inspiration of 5%  $\text{CO}_2$  during the control phase of hypercapnia nor the administration of the unknown drug caused significant changes in either BP or HR. However, both BP and HR demonstrated a nonsignificant elevation, approximately 14 mmHg and 18 beats/min, respectively, following administration of ketamine. This rise was most noticeable after the first ketamine dose and appeared to be attenuated by morphine.

After the third ketamine dose, two subjects were unresponsive to verbal stimuli (placebo session and high-dose morphine sulfate session). All subjects were unresponsive to verbal stimuli after the fourth dose (cumulative

dose 1.7 mg/kg) and remained so for 10–15 min after the last (fifth) dose.

### VENTILATION

Respiration remained adequate in all subjects throughout the sessions. However, several subjects were unable to keep the mouthpiece properly placed. In these instances, usually after the fourth ketamine dose, an anesthesia mask was substituted and jaw support provided when necessary.

At the beginning of the isohypercapnic phase, after breathing 5% inspired  $\text{CO}_2$  for 8 min, average  $\text{PET}_{\text{CO}_2}$  was  $49.8 \pm 2.4$  mmHg (mean  $\pm$  SD), which was  $6.1 \pm 0.3$  mmHg above resting  $\text{PET}_{\text{CO}_2}$ . During isohypercapnia we controlled  $\text{PET}_{\text{CO}_2}$  within approximately 1 mmHg of the target value. During isohypercapnia, ketamine alone appeared to cause a dose-related decrease in  $\dot{V}_E$  (fig. 1). There was no detectable change in the  $\text{CO}_2$  response curve slope after 3 mg/kg ketamine (table 1). The respiratory depression observed during isohypercapnia was a reflection of a 2 mmHg parallel displacement of the  $\text{CO}_2$  response curve observed both at the end of the ketamine injections ( $P = 0.057$ , not significant) and 1 h later (tables 1 and 2). The respiratory depression can be quantitated as either a 2 mmHg rightward displacement (table 2) or as an isohypercapnic decrease in  $\dot{V}_E$  of 4 l/min.

Both doses of morphine caused significant decreases in  $\dot{V}_E$  during isohypercapnia (fig. 1). Ketamine given after either dose of morphine caused additional decreases in  $\dot{V}_E$  similar to the effects of ketamine alone, that is, an apparent dose-related depression of respiration. The combination of ketamine and morphine caused rightward (or downward) displacement of the  $\text{CO}_2$  response curves without significant changes in slope, both immediately

after the last dose of ketamine and 1 h later (tables 1 and 2).

The slope of the ketamine dose *versus* ventilation curve was not significantly affected by either of the morphine pretreatments. Each of the three slopes in figure 1 was significantly different from zero but not from each other. At constant  $PET_{CO_2}$  the overall regression of ventilation ( $\dot{V}_E$  in l/min) on ketamine dose in mg/kg was:

$$\dot{V}_E = -2.31(\text{Ln}[\text{dose}]) + C.$$

C is a constant depending on both pretreatment and  $PET_{CO_2}$ , that is, the initial conditions. Over the dose range studied, doubling the ketamine dose decreased  $\dot{V}_E$  by  $1.6 \pm 0.3$  l/min at constant  $PET_{CO_2}$ . This is in contrast with the effect of morphine, where doubling the dose caused  $\dot{V}_E$  to decrease  $7 \pm 0.8$  l/min, which is typical for potent opioids used for premedication.<sup>§</sup>

The morphine-related respiratory depression was caused by decreases in both tidal volume ( $V_T$ ) and respiratory frequency (f). The decrease in  $\dot{V}_E$  caused by ketamine either alone or after morphine appeared to be caused more by decreases in  $V_T$  than reductions in f.

### Discussion

Our data indicate that in humans, ketamine alone causes a log-linear, dose-related depression of ventilation. This depression is similar to that seen with narcotics in the premedicant or analgesic dose range in that the slope of the ventilatory response to  $CO_2$  is unchanged, while the response curve is shifted to the right.<sup>19</sup> Ketamine administered after morphine appeared to have an additive effect that caused a dose-related reduction in  $\dot{V}_E$  due to a further rightward displacement of the  $CO_2$  response curve without a detectable change in slope. These effects persisted throughout the duration of our study (*i.e.*, approximately 2 h after the first ketamine dose and 1½ h after the last dose).

Ketamine's effect on  $CO_2$ -mediated control of respiration, a rightward displacement of the  $CO_2$  response curve without a change in slope, is similar to the effect of narcotics and is distinctly different from virtually all anesthetics and hypnotics,<sup>20-23</sup> which not only displace the response curve, but also decrease the slope. Ketamine depresses ventilation but, like morphine, does not reduce the respiratory response to increasing levels of  $CO_2$ . When studied by the steady-state technique,<sup>24</sup> cats demonstrate a similar parallel shift in the  $CO_2$  response curve after receiving ketamine. These characteristics remain in the presence of previously administered morphine over the dose range we studied. Whether ketamine would cause similar additive effects in the presence of other respiratory depressants, particularly the benzodiazepines, barbiturates, or inhalational anesthetics, is speculative.

§ Smith TC, unpublished data.

TABLE 1.  $CO_2$  Response Curve Slope  
( $l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ , mean  $\pm$  SEM)

Ketamine and:	Before Unknown	15 min after Last Ketamine	1 h after Last Ketamine
Placebo	1.76 $\pm$ 0.23	2.13 $\pm$ 0.47	1.73 $\pm$ 0.18
Morphine 0.2 mg/kg	1.68 $\pm$ 0.19	1.70 $\pm$ 0.19	1.51 $\pm$ 0.20
Morphine 0.4 mg/kg	2.34 $\pm$ 0.31	2.16 $\pm$ 0.36	2.02 $\pm$ 0.30

No postdrug values are significantly different from the respective control values. The three control values are not significantly different.

TABLE 2. The  $CO_2$  Response Curve Position  
( $PET_{CO_2}$ , mmHg, mean  $\pm$  SEM at  $\dot{V}_E = 15$  l/min)

Ketamine and:	Before Unknown	15 min after Last Ketamine	1 h after Last Ketamine
Placebo	47.7 $\pm$ 1.3	49.7 $\pm$ 1.3†	49.7 $\pm$ 1.1*
Morphine 0.2 mg/kg	48.7 $\pm$ 1.5	59.0 $\pm$ 1.7*	57.4 $\pm$ 2.0*
Morphine 0.4 mg/kg	47.5 $\pm$ 2.1	58.2 $\pm$ 2.4*	58.0 $\pm$ 2.3*

\* Significantly different from respective control value ( $P < 0.05$  for multiple comparisons).

†  $P = 0.057$ .

We do not know the mechanism of ketamine's effect on respiratory control. However, there is ample evidence that low-dose ketamine is an analgesic,<sup>7,25</sup> and there is accumulating evidence that this analgesia is mediated by opioid receptors<sup>26-29</sup> and that it can be antagonized by naloxone.<sup>27,28</sup> Because ketamine almost certainly acts on the opioid receptors mediating antinociception and because the respiratory depression caused by ketamine so closely resembles that caused by narcotics, it is reasonable to speculate that ketamine's effect on respiration might also be mediated by opioid receptors. Although the opioid receptors for analgesia and respiration may be different,<sup>30,31,¶</sup> virtually all clinically available narcotic analgesics act on multiple receptors causing inseparable analgesia and respiratory depression. Further, narcotics usually cause measurable analgesia at low doses when respiratory depression is difficult to detect, although measurable if clinically insignificant respiratory depression may outlast analgesia.¶ Although our study did not specifically address this issue, the evidence favors the opioid receptors as the site at which low-dose ketamine causes respiratory depression.

The maintenance of a normal  $CO_2$  response curve slope with the loss of responsiveness is unique to ketamine. A decrease in the level of consciousness invariably causes a decrease in the slope of the  $CO_2$  response curve whether due to large-dose opioid anesthesia<sup>32</sup> or other agents such as barbiturates,<sup>33</sup> benzodiazepines,<sup>34</sup> inhalational anes-

¶ Smith AA, Albin R, Crofford M: Heterogeneity of receptors for analgesia respiration and lenticular effect in opiates and endogenous opioid peptides. Proceedings of the International Narcotics Research Club Meeting, Aberdeen, UK, July 19-22, 1976. Amsterdam, Elsevier/North Holland, 1976, pp 289-294.

thetics,<sup>9</sup> or sleep itself.<sup>35</sup> This distinction emphasizes the differences between the loss of responsiveness state caused by ketamine and may imply that the loss of consciousness during opioid anesthesia is mediated by a mechanism or by receptors different from those that mediate analgesia or respiratory depression.<sup>36</sup>

Our results show that ketamine is a mild respiratory depressant with effects on the CO<sub>2</sub> response curve that are similar to but of lesser degree than analgesic doses of morphine. This effect is additive with morphine. Ketamine's respiratory effects may be mediated by opioid receptors as its analgesic effects seem to be. If this is the case, in view of the evidence that naloxone antagonizes ketamine-associated analgesia, naloxone may also antagonize the respiratory depression caused by ketamine. One of the authors is investigating this possibility.

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