Ventilatory Response to CO₂ Following Intravenous Ketamine in Children

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The effects of intravenous ketamine (bolus of 2 mg · kg⁻¹ followed by a continuous infusion at a rate of 40 µg · kg⁻¹ · min⁻¹) on ventilatory response to carbon dioxide were studied in nine children ranging in age from 6 to 10 yr and in weight from 20 to 48 kg. Ketamine did not affect resting respiratory rate, tidal volume, end-tidal CO₂ tension (PETCO₂), or minute ventilation. Five minutes after the ketamine bolus, the slope VE/PETCO₂ decreased significantly (P < 0.05) from 1.71 ± 0.47 to 1.05 ± 0.23 l · min⁻¹ · mmHg⁻¹ (mean ± SD). After 30 min of continuous iv ketamine infusion, the slope returned to 1.65 ± 0.44 l · min⁻¹ · mmHg⁻¹, a significantly higher value (P < 0.05) compared with the nadir and not significantly different from control. The minute ventilation at a PETCO₂ of 50 mmHg decreased from 824 ± 98 to 626 ± 26 ml · kg⁻¹ · min⁻¹ 5 min after iv ketamine, and remained depressed (640 ± 125 ml · kg⁻¹ · min⁻¹ P < 0.05) throughout the 30-min ketamine infusion. In addition, the slope VT/PETCO₂ and the VT 60 did not change during the study; nonetheless, the slope f/PETCO₂ and the f 60 decreased significantly following iv bolus ketamine, and the f 60 remained significantly decreased following ketamine infusion. The authors conclude that clinically useful doses of iv ketamine significantly alter ventilatory control in children. (Key words: Analgesics: ketamine. Anesthesia: pediatric. Anesthetics, Intravenous: ketamine. Ventilation: carbon dioxide response.)

KETAMINE IS FREQUENTLY USED FOR ANESTHESIA IN CHILDREN AS UNPLEASANT EMERGENCE REACTIONS OCCUR LESS FREQUENTLY IN CHILDREN THAN IN ADULTS.10 ALTHOUGH KETAMINE INITIALLY WAS REPORTED TO BE DEVOID OF RESPIRATORY DEPRESSANT EFFECTS,1,2 THIS CONCEPT HAS BEEN CHALLENGED BY EVIDENCE FROM STUDIES IN ANIMALS3,4,6 AND, MORE RECENTLY, IN ADULT HUMANS5 THAT DEMONSTRATES THAT KETAMINE DECREASES THE VENTILATORY RESPONSE TO CO₂. OTHER RECENT STUDIES USING NONINVASIVE METHODS DEMONSTRATED MAINTENANCE OF FRC AND MINUTE VENTILATION7 AND INCREASED MINUTE VENTILATION8 AFTER IV KETAMINE IN ADULTS. THE MAINTENANCE OF FRC AFTER IV KETAMINE HAS BEEN SHOWN ALSO IN CHILDREN.9 However, despite several clinical reports of apnea10,11 or hypoxemia12 following use of iv ketamine, there is little information regarding its effect on ventilatory control in children. We designed the present study to evaluate the effect of a bolus injection followed by continuous infusion of ketamine on ventilatory control in children.

Materials and Methods

PATIENTS

Nine ASA physical status I children, aged 9.1 ± 1.3 yr (mean ± SD; range 6–10 yr) and weighing 34.1 ± 8.1 kg (range 20–48 kg) were studied. This study was approved by the Human Investigation Committee and parental consent was obtained. The children were scheduled to undergo lower abdominal or minor reconstructive surgery. All had fasted 6 h before anesthesia and none had received atropine or other premedication.

ANESTHETIC PROCEDURE

Heart rate, ECG, and arterial pressure, measured with an automated blood pressure cuff, were continuously monitored. After an iv infusion of 5% dextrose in 0.2% NaCl was started, anesthesia was induced with ketamine, 2 mg · kg⁻¹, injected intravenously over a 1-min period and maintained for the next 30 min with a continuous iv infusion of ketamine, 40 µg · kg⁻¹ · min⁻¹. At the end of the study, anesthesia was supplemented as needed (e.g., caudal block), and surgery was performed.

VENTILATORY MEASUREMENTS

Respiratory rate (f), tidal volume (VT), minute ventilation (VE), and end-tidal CO₂ tension (PETCO₂) were recorded during room-air breathing and CO₂ rebreathing with a face mask through a pneumotachograph (Fleisch no. 1 for children younger than 8 yr, Fleisch no. 2 for children 8 yr or older) and a Rudolph nonbreathing valve. Instrument dead space was 45 ml in the children younger than 8 yr and 70 ml in the children older than 8 yr. The inspiratory and expiratory resistances of the system are, respectively, 2.4 and 3.6 cm H₂O · s⁻¹ · l⁻¹ at a flow of 1 l/s. VE response to CO₂ was assessed by rebreathing for 5 min from a 3–5-l spirometer filled with 7% CO₂ in oxygen. Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven, Holland) connected to the pneumotachograph previously calibrated with a 1-liter syringe of air. End-tidal CO₂ tension was measured with a continuously sampling Godart capnograph (Bilthoven, Holland) calibrated before and
after each measurement with 5% and 7% CO\textsubscript{2} in O\textsubscript{2}. Calibration gases were verified to be within 1% of the indicated value using Scholander microanalysis. Pneumotachograph and capnograph outputs were interfaced to a CM8 SX64 computer with an analog-to-digital converter. Linear regression equations were computed from VE, VT, f, and PETCO\textsubscript{2} for each CO\textsubscript{2} challenge curve. The correlation coefficient ranged from 0.95 to 0.99. The minute ventilation, the tidal volume, and the respiratory rate at PETCO\textsubscript{2} of 60 mmHg (VE60, VT60, f60) were calculated. We performed three CO\textsubscript{2} response curve measurements: 1) CONTROL, before induction of anesthesia, after a 5-min acclimatization period; 2) BOLUS, 5 min after the iv bolus of ketamine to assess the “bolus effect,” and 3) INFUSION, after 30 min of continuous iv infusion of ketamine to assess the effect of steady-state ketamine anesthesia.

**STATISTICAL ANALYSIS**

All values are expressed as the mean ± SD. Differences in respiratory variables were examined using repeated measures ANOVA followed by t tests corrected for multiple comparisons. P < 0.05 was considered statistically significant.

**Results**

**GENERAL**

None of the children experienced an unpleasant emergence reaction after surgery. Blood pressure and heart rate remained within 20% of control values and no cardiac arrhythmias occurred during the CO\textsubscript{2} rebreathing challenges. All children were unresponsive within 1 min after the end of iv bolus of ketamine and remained in this state throughout the study. In some instances, increased salivation was noted.

**VENTILATION**

None of the children developed apnea or cyanosis after the iv bolus of ketamine, and there were no airway problems during the study. The results of ventilatory measurements are summarized in table 1 and figure 1. Resting respiratory variables did not change during the study (table 1). Following the iv bolus injection of ketamine, there was a significant decrease in both the slope VE/PETCO\textsubscript{2} and the slope f/PETCO\textsubscript{2} and the VE60 and the f60 (table 2). In contrast, after 30 min of continuous infusion of ketamine, VE60 and f60 remained significantly depressed but the slope VE/PETCO\textsubscript{2} had significantly increased and returned to its control value; the value of the slope f/PETCO\textsubscript{2} after 30 min of continuous infusion of ketamine was not significant from control and iv bolus ketamine values (table 2). In addition, the slope VT/PETCO\textsubscript{2} and the Vt 60 did not change significantly during the study (table 2). Figure 1 demonstrates the evolution of the slope VE/PETCO\textsubscript{2} during the study.

**Discussion**

This study shows that, in children as in adults, ketamine induces respiratory depression. During spontaneous breathing of room air, the control resting f, VT, and VE values of the children were somewhat higher than the normal value expected for their age. This was probably related in part to their anxiety, as suggested by the low PETCO\textsubscript{2}, but also to the relatively high dead space of our apparatus. However, we believe that the latter, a well-known methodological problem with pneumotachography, is acceptable in our study as each patient served as his/her own control. The resting ventilatory variables were unchanged by ketamine anesthesia; this result is consistent with the maintenance of minute ventilation re-

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**Table 1. Resting Respiratory Variables (Mean ± SD) before Ketamine (CONTROL) 5 Min after iv Bolus of Ketamine (BOLUS) and 30 Min after Continuous iv Infusion of Ketamine (INFUSION)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Bolus</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting f (breaths/min)</td>
<td>26.0 ± 7.2</td>
<td>23.3 ± 4.6</td>
<td>25.1 ± 6.1</td>
</tr>
<tr>
<td>Resting VT (ml·kg\textsuperscript{-1})</td>
<td>8.7 ± 1.3</td>
<td>9.0 ± 2.1</td>
<td>7.7 ± 2.1</td>
</tr>
<tr>
<td>Resting VE (ml·kg\textsuperscript{-1}·min\textsuperscript{-1})</td>
<td>207 ± 65</td>
<td>185 ± 45</td>
<td>175 ± 60</td>
</tr>
<tr>
<td>Resting PETCO\textsubscript{2} (mmHg)</td>
<td>34.5 ± 4.2</td>
<td>36.7 ± 3.8</td>
<td>36.3 ± 3.9</td>
</tr>
</tbody>
</table>

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**FIG. 1. Changes in the slopes of the CO\textsubscript{2} responses curves.**

*P < 0.05 versus control value.*
TABLE 2. Respiratory Variables during CO₂ Challenge Curve (Mean ± SD) before Ketamine (CONTROL) 5 Min after iv Bolus of Ketamine (BOLUS) and 30 Min after Continuous iv Infusion of Ketamine (INFUSION)

<table>
<thead>
<tr>
<th>Slope VE/PETCO₂ (l·min⁻¹·mmHg⁻¹)</th>
<th>Control</th>
<th>Ketamine</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.71 ± 0.47</td>
<td>1.05 ± 0.23*</td>
<td>1.65 ± 0.44†</td>
<td></td>
</tr>
<tr>
<td>VE 60 (ml·kg⁻¹·min⁻¹)</td>
<td>824 ± 98</td>
<td>626 ± 26*</td>
<td>640 ± 125*</td>
</tr>
<tr>
<td>Slope VT/PETCO₂ (ml·mmHg⁻¹)</td>
<td>25.4 ± 12</td>
<td>28.2 ± 7.7</td>
<td>28.1 ± 12.0</td>
</tr>
<tr>
<td>VT 60 (ml·kg⁻¹)</td>
<td>24.3 ± 7.6</td>
<td>25.4 ± 5.9</td>
<td>25.1 ± 5.3</td>
</tr>
<tr>
<td>Slope f/PETCO₂ (breaths·min⁻¹, mmHg⁻¹)</td>
<td>1.59 ± 0.81</td>
<td>0.54 ± 0.23*</td>
<td>0.84 ± 0.55</td>
</tr>
<tr>
<td>f 60 (breaths·min⁻¹)</td>
<td>48 ± 17</td>
<td>33 ± 9*</td>
<td>37 ± 17*</td>
</tr>
</tbody>
</table>

* P < 0.05 vs. control value.
† P < 0.05 vs. bolus value.

ported in adults as measured by a noninvasive method. In addition, Shulman et al. have reported the maintenance of FRC during ketamine anesthesia in children. Therefore, adequate gas exchange during unobstructed spontaneous room air breathing should be expected after ketamine.

In addition, we found that an intravenous bolus of ketamine significantly decreased the slope of the CO₂ response curve; this response disappeared after 30 min of ketamine infusion, although the VE60 remained depressed. These results are in agreement with those of Clergue et al.; who reported a similar decrease in slope and VE60 soon after an iv bolus of ketamine, 2 mg·kg⁻¹, in adults. Moreover, Hirshman et al. reported a decrease in the slope of the CO₂ response curve in dogs after a ketamine bolus of 10 mg·kg⁻¹, but, unfortunately, neither the rate of ketamine infusion nor the time at which the CO₂ rebreathing test was done were indicated. In contrast, Jaspar et al. studied the ventilatory response to CO₂ approximately 20 min after a ketamine bolus and found no decrease in the slope of the ventilatory response to CO₂ when compared with control; however, these authors found a decrease in the occlusion pressure following ketamine bolus administration. In adults, Bourke et al. administered five logarithmically scaled doses of iv ketamine at 10-min intervals (total dose 3 mg·kg⁻¹) and found a dose-related decrease in VE but without a significant change in the slope of the CO₂ response curve. These apparently contradictory results can be explained by the pharmacokinetics of iv ketamine. Idvall et al. determined the pharmacokinetics of ketamine in adults after an iv bolus of 2 mg·kg⁻¹ followed by a continuous iv infusion at a mean rate of 41 ± 21 μg·kg⁻¹·min⁻¹ (these dosages are similar to those that we used in this study). They found a mean plasma concentration of ketamine of 60 nmol·l⁻¹ 5 min after a bolus injection which decreased to 9 nmol·l⁻¹ after 20 min of ketamine infusion and remained stable at this level during ketamine infusion for at least 1 h. Although we did not measure plasma concentration of ketamine, and although we studied children rather than adults, it is likely that the ratios of plasma concentrations of ketamine 5 min and 30 min after the iv bolus in our patients were similar to those reported by Idvall et al. Therefore, it appears that the clearly different effect of ketamine on the slope of the CO₂ response curves measured 5 and 30 min after bolus injection is related to this difference in plasma concentration. An objection to CO₂ rebreathing test (requiring 4–5 min) is that plasma ketamine levels no doubt decrease between 5 and 10 min after iv bolus injection. However, the steady-state multiple concentration CO₂ response method, which is theoretically better for bolus drug studies, is impractical in children, because of the long period of equilibration that is needed. We, therefore, decided to use the CO₂ rebreathing test, a more acceptable test in children, despite the inevitable methodological problem it presents. It is important to note that the effect of a decrease in drug level between 5 and 10 min after iv bolus administration would be theoretical; in fact, the brain tissue concentration was probably not changed. Despite this, there was, in fact, a significant decrease in the slope of the CO₂ response curve after the iv bolus of ketamine compared with both the "control" and the "infusion" value. A similar "dual" effect of an anesthetic agent was reported by Gross et al. with thiopental and midazolam as well as with lidocaine. With the later drug, transient ventilatory depression was observed concomitantly with a peak in the plasma concentration that may have desensitized the ventilatory control centers or which may due to a delayed redistribution. This may also be the case after the iv bolus of ketamine, thus explaining the transient decrease in slope that we observed. We believe our results may provide a rational basis for some clinical reports of prolonged apnea following iv bolus injection of ketamine in young children and infants. In addition, our study shows that, in children as in adults, the ventilatory depressant effect of a continuous infusion of ketamine (steady-state) is similar to that observed with analgesic dose of morphine: i.e., a shift to the right of the CO₂ response curve without a change in the slope. These qualitatively similar effects of ketamine and opioids on respiratory control may be mediated by opioid receptors. In addition, the fact that the respiratory depression was principally due to a decrease in the respiratory rate, rather than a decrease in tidal volume, adds further support to the fact that ketamine...
may act similarly to morphine at an opiate receptor. It is, therefore, not surprising that we observed normal resting respiratory values with a decrease in responsiveness of the respiratory center to CO₂ in our study, as has been reported following opioids in children.¹⁷

In conclusion, ketamine is a respiratory depressant in children, particularly after an iv bolus injection. These data emphasize the importance of being able to provide ventilatory support when this agent is used in children. Our results suggest that, to minimize respiratory depression, ketamine should be administered iv at a slow rate, rather than by rapid bolus injection. We believe that further studies are needed to correlate plasma levels of ketamine with its respiratory effects.

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References

11. Lockart CH, Jenkins JJ: Ketamine induced apnea in patients with increased intracranial pressure. ANESTHESIOLOGY 37:92–93, 1972