The Effect of Lidocaine on the Ventilatory Response to Carbon Dioxide

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The authors determined the effect of intravenous lidocaine, both as a bolus and as an infusion, on the ventilatory response to CO₂. Bolus injection of 1.5 mg/kg lidocaine caused a decrease in the slope of the CO₂ ventilatory response curve from 2.66 ± 0.30 (± SEM) to 1.31 ± 0.44 1·min⁻¹·mmHg⁻¹ within 90 s; the effect was transient, with slope returning to 2.59 ± 0.85 1·min⁻¹·mmHg⁻¹ 150 s after injection. The transient, subconvulsive lidocaine concentrations present during ventilatory depression (0.9 ± 2.0 µg/ml) may be sufficient to desensitize the medullary ventilatory control centers.

Lidocaine infusion at the rate of 60 µg·kg⁻¹·min⁻¹ (serum lidocaine concentrations of 3.5 ± 0.2 µg/ml) increased the slope of steady state CO₂ response curves from 2.89 ± 0.29 to 4.17 ± 0.44 1·min⁻¹·mmHg⁻¹ (P < 0.05); with discontinuation of the infusion, slope returned to 3.18 ± 0.33 1·min⁻¹·mmHg⁻¹ (P < 0.05). The authors conclude that bolus injection of lidocaine transiently can depress ventilatory control, however, rapid redistribution of lidocaine makes this a transient phenomenon that can be treated with supplemental oxygen if necessary. The increased CO₂ sensitivity observed during lidocaine infusion suggests that studies of ventilatory control in patients receiving anesthesia must take into account the direct effect of absorbed anesthetics on ventilatory control. (Key words: Anesthetics, local: lidocaine. Carbon dioxide: ventilatory response. Ventilation: carbon dioxide response.)

LIDOCAINE, an amide local anesthetic, is used widely in medical practice to provide conduction anesthesia, to control myocardial irritability, and as an adjunct to general anesthesia. Although the cardiovascular and central nervous system effects of lidocaine have been investigated extensively, there are few studies of the effects of lidocaine or other local anesthetics on ventilatory control in humans. While lidocaine has been shown to depress ventilation in dogs and humans during general anesthesia, previous studies of the effect of lidocaine on ventilatory control in awake man have been inconclusive. To clarify the influence of lidocaine on ventilatory control, we determined the effect of a lidocaine infusion on the ventilatory response to carbon dioxide in healthy volunteers using steady state methods. Concurrently, we determined the time course of the ventilatory effect of a 1.5 mg/kg intravenous bolus of lidocaine using the recently described dual isohypercapnic technique.

Methods

Seven healthy male volunteers, aged 27 to 31 yr, consented to participate in our study, which was approved by our institutional review committees. Subjects refrained from caffeine- or alcohol-containing beverages for 12 h and took nothing by mouth for 8 h before their studies. On arrival in the laboratory, each subject was weighed, and intravenous and radial arterial catheters were inserted; directly measured arterial pressure as well as the electrocardiogram were monitored continuously. Normal saline was infused through the venous catheter at a rate of 100 ml/h.

A Godart Capnograph (R) was calibrated, using standard gas mixtures previously analyzed by microscholander analysis. An Electro/med 780 rolling seal spirometer was calibrated with a 2-l calibrating syringe. A Beckman C-2 paramagnetic oxygen analyzer insured an FiO₂ > 0.5 during the experiments.

The supine subjects listened to symphonic music through occlusive headphones as they breathed mixtures of CO₂ in O₂ through the circuit shown in figure 1. By adjusting the circuit, it was possible to maintain end-tidal CO₂ tension to within ±1 mmHg. Resistance to gas flow in the circuit was 0.02 cm H₂O·1⁻¹·min⁻¹. Oxygen was added to the system to meet metabolic requirements while maintaining a constant volume in the breathing circuit. The temperature of the bag-in-the-box was measured with a Yellow Springs Instruments 400 series thermistor; all volumes were converted to BTS with the use of standard formulas. The Capnograph and spirometer were interfaced to a CBM 8032 computer by a multichannel analog to digital converter.

Bolus Injection

After allowing 8 min for equilibration at an end-tidal P CO₂ of approximately 46 or 58 mmHg for alternate subjects, we measured minute ventilation as 1.5 mg/kg of lidocaine was injected intravenously over 15 s. By varying the speed of the circulator, we continuously adjusted flow through the CO₂ absorber to keep end-tidal P CO₂ constant as ventilation varied. Arterial blood samples for lidocaine
analysis were obtained at 1-min intervals for the first 5 min after injection; ventilatory measurements continued for 10 min after injection.

Ninety minutes after the first injection, the subjects were restudied; this time end-tidal CO₂ tension was maintained at 58 or 46 mmHg, the value not studied previously. To allow for the effects of residual lidocaine, the second bolus dose was reduced empirically by 5%. Arterial blood for lidocaine determination was obtained just before and at 1-min intervals after the second bolus.

CO₂ response curves were constructed for each subject before and at 20-s intervals after lidocaine injection. The slope of each curve is the difference between ventilation at high (58 mmHg) and low (46 mmHg) end-tidal CO₂ tensions divided by the difference in measured CO₂ tension.

Overall changes in slope with time were analyzed using two-way analysis of variance. Significance of slope changes at individual times after injection was determined by Student's t test with Bonferroni's correction for multiple comparisons. A value of P < 0.05 was taken as indicating statistical significance.

**Infusion**

Before the subjects received any lidocaine, four-point steady state CO₂ response curves were determined as follows. After 8 min for equilibration at an end-tidal PCO₂ of approximately 46 mmHg, minute ventilation was measured over 30 breaths. This process was repeated at end-tidal CO₂ tensions of approximately 50, 54, and 58 mmHg. From these data a preinfusion CO₂ response curve was determined for each subject by the method of least squares.

Ten minutes after the second lidocaine bolus of the dual-isohypercapnic study (vide supra), each subject received a 60 μg·kg⁻¹·min⁻¹ lidocaine infusion; this rate was chosen to give stable serum lidocaine concentrations near the upper limit of the therapeutic range within an hour. Ninety minutes after the start of the infusion, the steady state CO₂ ventilatory response measurement was repeated. Just prior to obtaining the first ventilatory measurement, and immediately upon completion of the test, 10-ml samples of arterial blood were obtained to determine the stability of lidocaine concentrations. The infusion then was discontinued.

One hour later, we repeated the CO₂ response measurement to rule out diurnal variation or the effects of repeated CO₂ exposure as a cause of any change observed during lidocaine infusion. An arterial sample for lidocaine analysis was obtained before the ventilatory measurement.

Slopes of the CO₂ response curves during lidocaine infusion were compared with the preinfusion and postinfusion control values using two-way analysis of variance and Tukey's test for multiple comparisons. Values of P < 0.05 were taken as indicating statistical significance.

**Lidocaine Assay**

Lidocaine assays were performed using the Emit-cad quantitative enzyme immunoassay technique (Syva, Palo Alto, California). This assay is optimally sensitive in the range of 1.0–12.0 μg/ml with a coefficient of variation of less than 5% in our laboratory.

**Results**

**Bolus Injection**

Lidocaine injection did not cause significant changes in heart rate, arterial pressure, or state of consciousness during the isohypercapnic determinations. For technical reasons, we were unable to complete isohypercapnic data...
acquisition for one subject; therefore, the results reported are those of the remaining six subjects.

The mean calculated slope of the CO\textsubscript{2} response curves before lidocaine injection (time 0) was 2.66 ± 0.30 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1} (\bar{X} ± SEM), within the normal range reported elsewhere.\textsuperscript{14} Following injection of lidocaine, there was a rapid decrease in the slope of the CO\textsubscript{2} response curve, reaching a minimum of 1.51 ± 0.44 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1} 90 s after injection (0.05 < P < 0.10). This decrease was transient; the slope had returned to 2.39 ± 0.83 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1} by 150 s after injection (fig. 2). The change in slope with time was highly significant (P < 0.005, F = 3.51), although this significance could not be attributed to the change in slope at any single time.

Serum lidocaine levels obtained during the first five minutes after injection are shown in figure 3. It is clear that the injection sequence did not affect the resulting serum lidocaine levels, which is not unexpected because serum levels just before the second bolus were less than 0.5 µg/ml.

**Infusion**

The control steady-state slope of the CO\textsubscript{2} response curve was 2.89 ± 0.29 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1}, which is comparable to the control value obtained during the dual isohypercapnic determination (vide supra) (table 1). During lidocaine infusion, the mean serum lidocaine concentrations were 3.5 ± 0.2 µg/ml, which is within the therapeutic range for treatment of ventricular arrhythmias.\textsuperscript{13} Individual subjects' levels varied by less than 0.5 µg/ml during steady state ventilatory response determination. During infusion, the slope of the CO\textsubscript{2} response curve increased to 4.17 ± 0.44 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1}. This change in slope was statistically significant (P < 0.05). One hour after discontinuation of lidocaine infusion, the mean serum lidocaine concentration was 1.4 ± 0.2 µg/ml. At this time the slope of the CO\textsubscript{2} response curve was 3.18 ± 0.33 l·min\textsuperscript{-1}·mmHg\textsuperscript{-1}. This slope was significantly different from that observed during lidocaine infusion and similar to the preinfusion value (fig. 4).

**Discussion**

We have demonstrated that an intravenous bolus of lidocaine causes significant but transient depression of the ventilatory response to hypercapnia, while therapeutic steady state lidocaine concentrations increase the response to hypercapnia in healthy, unmedicated volunteers. These findings have not been described previously.

In their recent abstract, Camporesi and Neilsen\textsuperscript{16} reported that a 1.5 mg/kg intravenous bolus of lidocaine caused no change in the slope of the CO\textsubscript{2} response curve. Their failure to demonstrate a change in slope probably resulted in part from the fact that their measurements were made 5–10 min after lidocaine injection, when serum drug levels were subtherapeutic (1.03 ± 0.11 µg/
The lidocaine concentrations reported during infusion are the mean of values obtained just before and just after ventilatory response determination. For technical reasons, postinfusion ventilatory response and lidocaine concentration data were unobtainable for subject 6.

To overcome this methodologic problem, we used the dual-isohypercapnic technique to evaluate the effect of a lidocaine bolus on ventilatory control.\(^{11,12}\) Because we were able to determine the slope of the CO\(_2\) response curve as frequently as every 20 s, we demonstrated a transient decrease in the ventilatory response to CO\(_2\) after lidocaine injection. Ventilatory depressant effects of lidocaine previously have been reported in anesthetized dogs\(^{6}\) and humans.\(^{7,8}\) Our results suggest that the relatively high serum lidocaine concentrations observed during the first minutes after lidocaine bolus injection have a similar effect in unmedicated volunteers.

To evaluate the effect of steady state therapeutic lidocaine concentrations on ventilatory control, we used the steady-state CO\(_2\) rebreathing technique. In contrast to our observations after bolus administration, we found an increase in the slope of the CO\(_2\) response curve during lidocaine infusion. Because control and postinfusion slopes were similar, and because both were significantly different from the slope during infusion, it is unlikely that this was the result of diurnal variation or repeated CO\(_2\) breathing.

That lidocaine should cause an increase in the ventilatory response to hypercarbia is not unexpected. It is well known that lidocaine causes central nervous system excitation as well as depression, as evidenced by the seizures that result from overdoses. de Jong and co-workers\(^{15}\) reported enhanced spinal monosynaptic transmission following intravenous lidocaine, suggesting that the drug releases 2-neuron spinal reflex arcs from inhibitory control by depressing interneurons of the polysynaptic reflex arc. Mori and Fukuda\(^{16}\) showed that lidocaine selectively blocks inhibitory neurons in the midbrain reticular formation of the rat, thus facilitating spontaneous neuronal discharge in those neurons under strong inhibitory control.

Lidocaine and other local anesthetics also have been reported to exert a dual effect on the central nervous system manifested by an initial selective depression of inhibitory pathways leading to unopposed excitatory ac-

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**Table 1. Ventilatory Response and Serum Lidocaine Concentrations before, during, and after Lidocaine Infusion**

<table>
<thead>
<tr>
<th>Subject</th>
<th>CO(_2) Response Curve Slope ((\text{I-min}^{-1}\cdot\text{mmHg}^{-1}))</th>
<th>Serum Lidocaine Concentration ((\mu\text{g/ml}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinfusion Infusion Postinfusion Preinfusion Infusion Postinfusion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.96 3.84 3.97 2.9 1.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.99 5.76 3.37 3.0 1.0</td>
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</tr>
<tr>
<td>3</td>
<td>3.26 4.53 2.92 3.3 1.3</td>
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<tr>
<td>4</td>
<td>1.45 1.95 1.68 4.0 1.6</td>
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</tr>
<tr>
<td>5</td>
<td>3.07 5.00 3.60 3.4 1.3</td>
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<tr>
<td>6</td>
<td>2.51 4.14 — 3.3 —</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.08 4.00 3.57 4.4 2.4</td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>2.89 ± 0.29 4.17 ± 0.44 3.18 ± 0.33 3.5 ± 0.2 1.4 ± 0.2</td>
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</tbody>
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**Fig. 4.** Effect of lidocaine infusion on the steady state ventilatory response to CO\(_2\). Slope values during infusion were significantly greater than both the control and postinfusion slopes \((P < 0.05)\). Values are means ± SEM.
tivity, followed by generalized CNS depression at higher serum concentrations. Seo and coworkers recently have shown that lidocaine has a multiphasic, dose-dependent action on the CNS of cats. Early EEG manifestations included an initial period of reticular depression, followed by a stage of reticular and amygdaloid excitation. Although cross-species comparisons may be misleading, it is conceivable that this stage of “excitation” is the counterpart of the increased CO₂ sensitivity we observed during lidocaine infusion. Seo found that these stages were followed by a second period of CNS depression, which was terminated abruptly by the onset of seizure activity; the transient ventilatory depression we observed following bolus injection of lidocaine may correspond to the pre-seizure depressive phase noted in cats. Interestingly, peak serum lidocaine concentrations after bolus injection in our volunteers were within the pre-seizure range reported by others.

Following bolus injection, distribution of lidocaine in the brain reflects regional blood flow, with maximum tissue levels developing in highly perfused regions. On the other hand, steady state infusion would be expected to result in preferential distribution of lidocaine to those portions of the brain where its solubility is greatest. Therefore, the relationship between lidocaine concentrations in different parts of the brain depends upon the method of administration. It is possible that the relative distribution of lidocaine to various regions of the brain may determine the overall effect of the drug on ventilatory control. Thus, disparate effects may be observed, despite similar serum concentrations, providing an alternate explanation for our results.

Our findings may be relevant to certain clinical situations. Serum lidocaine concentrations after intercostal block are similar to those we observed after bolus injection, while serum lidocaine concentrations after epidural block are similar to those we observed during lidocaine infusion. Our results suggest that absorbed lidocaine might have an effect on ventilatory control following administration of certain regional blocks.

The respiratory depressant effect of an intravenous injection of lidocaine is transient, lasting only about 2.5 min after a 1.5 mg/kg bolus. Therefore, the practitioner can be assured reasonably that in the absence of seizure activity or cardiovascular dysfunction, respiratory depression will be short lived and managed easily with supplemental O₂ and ventilatory assistance. However, clinical evidence suggests that the ventilatory depressant effects of lidocaine may be potentiated by other CNS depressants and that the results of this study should not be extrapolated to heavily sedated patients. Furthermore, it is apparent from our results that investigations of the effects of regional block techniques on ventilatory control must consider the direct effects of absorbed local anesthetics.

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References