Ventilatory Response to CO\textsubscript{2} Following Intravenous and Epidural Lidocaine

Thierry Labaillé, M.D.,* François Clerge, M.D.,† Kamran Samii, M.D.,‡ Claude Eccoiffy, M.D.,§ Alain Berdeaux, Pharm.D.¶

The authors determined the effects of intravenous infusion and epidural administration of lidocaine on the control of ventilation in two groups of eight healthy unpremedicated subjects. In the intravenous group, an injection of 1.5 mg/kg lidocaine was followed by an infusion at a rate of 60 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} for 30 min. The slope of the ventilatory response to CO\textsubscript{2} was significantly increased (P < 0.05) from its control value (2.65 ± 1.22 1·min\textsuperscript{-1}·mmHg\textsuperscript{-1} [mean ± SD]) at the end of the infusion (58%), while plasma lidocaine level was at 3.14 ± 0.82 μg/ml. The correlation between individual plasma lidocaine levels and the changes in the slope of the ventilatory response to CO\textsubscript{2} was significant (r = 0.58, n = 24, P < 0.01). In the epidural group, after the administration of 5 mg/kg of lidocaine, the slope of the ventilatory response to CO\textsubscript{2} increased significantly (P < 0.05) from its control value (1.52 ± 0.75 1·min\textsuperscript{-1}·mmHg\textsuperscript{-1}) at 15 (+22%) and 25 min (+42%), while plasma lidocaine levels were at 1.79 ± 0.42 and 2.22 ± 0.47 μg/ml, respectively. In both groups, resting minute ventilation and end-tidal CO\textsubscript{2} values remained unchanged. These results suggest that epidural lidocaine has a stimulating effect on the ventilatory control mechanisms that results from the systemic effect of the drug. (Key words: Anesthesics, local: lidocaine. Anesthetic techniques: epidural. Ventilation: carbon dioxide response.)

It is generally agreed that uncomplicated epidural anesthesia has no consistent effect on ventilation. However, no data are available concerning the effect of epidural anesthesia on the ventilatory response to carbon dioxide. Epidural administration of local anesthetics is followed by systemic absorption of the drug and by spinal nerve blockade, both of which may interfere with the control mechanisms of ventilation. It has been shown that when lidocaine is administered intravenously at a constant rate, it induces a prolonged increase in plasma lidocaine concentration and an increase in the slope of the ventilatory response to CO\textsubscript{2}. However, the effects of epidural anesthesia are not only those obtained through the systemic absorption of the drug. The neural blockade may also interrupt both the afferent and efferent pathways between the respiratory centers and the peripheral respiratory system. Eisele et al. did not find a change in the ventilatory response to carbon dioxide after chest wall block alone produced by spinal anesthesia. However, only two patients were included in their study. Therefore, this study was conducted in order to determine in two groups of subjects, the effect on the ventilatory response to CO\textsubscript{2} of intravenous and epidural administration of lidocaine, achieving comparable plasma concentrations.

Methods

The study protocol received institutional approval, and informed consent was obtained from all participants. Sixteen male ASA I subjects (eight volunteers and eight patients) were studied. None of them had clinical evidence of respiratory, cardiovascular, hepatic, or seizure disorders, and none of them received any medication prior to the study. All subjects had fasted and took no caffeine- or alcohol-containing beverages overnight. None had received any premedication.

Procedure for Administration of Intravenous Lidocaine

Intravenous lidocaine was administered in eight volunteers. Their mean (±SD) age, height, and weight were 32 ± 4 yr, 177 ± 5 cm, and 74 ± 10 kg, respectively. Venous catheters were inserted in each arm for infusion (lactated Ringer's solution, 100 ml/h) and blood sampling. After a resting period of 20 min, a control set of measurements was made. Thereafter, 1.5 mg/kg lidocaine was injected intravenously over a 5-min period, immediately followed by a continuous infusion of 60 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} lidocaine. This dose was chosen in order to obtain lidocaine plasma levels comparable with those obtained after regional blocks. Thirty minutes after the beginning of the lidocaine infusion another set of measurement was performed. The lidocaine infusion was then discontinued. Two other sets of measurements were performed 20 and 40 min after discontinuation of the lidocaine infusion.

* Assistant in Anesthesiology, Hôpital Bicêtre, Kremlin Bicêtre.
† Professor of Anesthesiology, Hôpital Pitie Salpêtrière, Paris.
‡ Assistant in Anesthesiology, Hôpital Bicêtre, Kremlin Bicêtre.
§ Resident in Anesthesiology, Hôpital Bicêtre, Kremlin Bicêtre.
¶ Assistant in Pharmacology, Hôpital Bicêtre, Kremlin Bicêtre.

Received from the Departments of Anesthesiology and Pharmacology, Bicêtre Hospital, Paris-South University, 94270 Kremlin Bicêtre, and from the Department of Anesthesiology of Pitie Salpêtrière Hospital, Paris V University, 75013, Paris, France. Accepted for publication March 26, 1985. Supported by grants from Paris City Council and MAPAR Bicêtre. Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, October 1983, and New Orleans, October 1984.

Address reprint requests to Dr. Labaillé: Département d’Anesthesiologie, Hôpital Bicêtre, 94270 Kremlin Bicêtre, France.
PROCEDURE FOR ADMINISTRATION OF EPI DURAL LIDOCAINE

Eight patients scheduled for orthopedic surgery were studied. Their mean age, height, and weight were 35 ± 12 yr, 171 ± 7 cm, and 62 ± 8 kg, respectively. An infusion of lactated Ringer’s solution was started, and an epidural catheter was inserted at L3–4 level. The patients remained in a quiet room for 20 min. A control set of measurements was then performed, and 5 mg/kg of a 2% lidocaine solution was injected epidurally over 1 min. Two other sets of measurements were performed 15 and 25 min later. Calculated mean arterial pressure (Diastolic pressure + [systolic pressure − diastolic pressure]/3), measured with a sphygmomanometer, was maintained within 5% of its control values with the infusion of 600 ± 70 ml of lactated Ringer’s solution. After the last set of measurements, the upper level of analgesia was detected by the pinprick method.

VENTILATORY MEASUREMENTS

In all the subjects, a CO₂ stimulation test was performed the day prior to the procedure in order to familiarize them with the experiment. Minute ventilation was measured during room-air breathing and during a CO₂ stimulation test by the Read’s rebreathing method. All the subjects were studied in a 30-degree head-up position.

The subjects breathed through a mouth-piece connected to a Fleisch® pneumotachograph. Inspiratory and expiratory lines were separated by a one-way valve. The dead space of the circuit was 75 ml. This relatively large dead space resulted in somewhat increased values for resting pulmonary ventilation. The resistances of the inspiratory and expiratory lines were, respectively, 2.4 and 3.6 cmH₂O • s • 1⁻¹ at a flow of 1 l/s. Volume was measured by electronically integrating the flow signal obtained from the pneumotachograph, which had been previously calibrated with a 1-l syringe of air, connected to a Godart® 17212 differential pressure transducer (Bilthoven-Holland). End-tidal CO₂ (PETCO₂) was measured with a Godart® capnograph (Bilthoven-Holland), which was calibrated before and after each measurement with two different gases (5 and 8% CO₂ in O₂) from calibrating tanks that were verified to be accurate within 1% of the assigned value. All signals were recorded on a paper recorder, using a paper speed of 12.5 mm/s. Total cycle durations were measured from the flow signal. Tidal volume (VT) was measured by integrating the flow signal. Respiratory frequency (f) and minute-ventilation (VE) were calculated from these values by analyzing and averaging breaths at 30-s intervals. During air breathing, a steady state was obtained after 5 min with a plateau of PETCO₂ values and all values presented represent the means of 10 breaths. For the rebreathing tests, the first 30–40 s were discarded until a linear increasing PETCO₂ phase was observed that began close to 50 mmHg of PETCO₂. For each of the subsequent 3–4 min, PETCO₂ and VE were calculated at 30-s intervals. Rebreathing was continued until PETCO₂ increased to 9% or until ventilation increased to 70 l/min, whichever occurred first. The linear regression equations were calculated for VE versus PETCO₂, by means of least-squares linear regression analysis. All the responses were linear, with a correlation coefficient (r) ranging between 0.93 and 0.99. Values were converted to body temperature and ambient pressure saturated with water vapor (BTPS).

PLASMA LIDOCAINE ANALYSIS

Plasma lidocaine levels were assayed in duplicate by the specific EMIT homogeneous enzyme immunoassay (Syva Biomerieux Laboratories) from venous blood samples taken just prior to each CO₂ rebreathing test. This method measures lidocaine between 1 and 12 μg/ml with a coefficient of variation based upon repeated measurements of the same sample of less than 10%.

STATISTICAL ANALYSIS

In each group, each subject was used as his or her own control. Differences between arterial pressure and respiratory variables at each time interval and control values were tested using two-way analysis of variance and then by applying the Bonferroni multiple comparison procedure. Differences between the two groups were tested with the use of the t-test for unpaired data. Differences were considered significant when P < 0.05. All values were expressed as mean ± SD. For the correlation between the slope VE/PETCO₂ and the plasma lidocaine level we have expressed the slope V̇/PETCO₂ as per cent change from control value because of the broad range of individual values of this variable in the population.

RESULTS

INTRAVENOUS LIDOCAINE

During intravenous lidocaine infusion, four subjects reported easier breathing during the ventilatory effort elicited by the CO₂ rebreathing maneuver. All subjects reported a feeling of sedation. The results of the ventilatory variables during room air breathing and CO₂ stimulation tests and of plasma lidocaine concentrations are shown in table 1. During and after lidocaine infusion,
TABLE 1. Ventilation during Intravenous Lidocaine. Respiratory Variables and Plasma Lidocaine Levels before (control), during, and after Intravenous Infusion of Lidocaine in Eight Subjects (mean values ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Infusion 30 min</th>
<th>20 Min</th>
<th>40 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting (\dot{V}E) (l/min)</td>
<td>10.9 ± 4.3</td>
<td>9.9 ± 3.6</td>
<td>10.6 ± 3.2</td>
<td>10.6 ± 3.9</td>
</tr>
<tr>
<td>Resting VT (ml)</td>
<td>699 ± 59</td>
<td>590 ± 47</td>
<td>600 ± 40</td>
<td>670 ± 32</td>
</tr>
<tr>
<td>Resting (f) (breaths/min)</td>
<td>16 ± 5</td>
<td>15 ± 2</td>
<td>16 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Resting PET(_{CO_2}) (mmHg)</td>
<td>38 ± 5</td>
<td>38 ± 3</td>
<td>37 ± 5</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Slope of (\dot{V}E/PET(_{CO_2}) (l·min(^{-1}·mmHg)^{-1})</td>
<td>2.65 ± 1.22</td>
<td>4.20 ± 1.62*</td>
<td>3.25 ± 1.32</td>
<td>2.73 ± 1.02</td>
</tr>
<tr>
<td>Plasma lidocaine level ((\mu g/ml))</td>
<td>Not detectable</td>
<td>3.14 ± 0.82</td>
<td>1.70 ± 0.58</td>
<td>1.17 ± 0.54</td>
</tr>
</tbody>
</table>

\(\dot{V}E\) = minute ventilation; VT = tidal volume; \(f\) = respiratory frequency; PET\(_{CO_2}\) = end-tidal CO\(_2\) tension.

* Values that are significantly different from control (\(P < 0.05\)).

resting \(\dot{V}E\), \(f\), VT, and PET\(_{CO_2}\) values remained unchanged. Thirty minutes after the onset of the lidocaine infusion, the slope \(\dot{V}E/PET\(_{CO_2}\) was significantly increased from its control value and then returned close to its control value 20 min and 40 min after its discontinuation. Considering all measured values, the correlation between the individual plasma lidocaine levels and the changes in the slope \(\dot{V}E/PET\(_{CO_2}\) was significant (\(r = 0.58\), \(n = 24\), \(P < 0.01\)) (fig. 1).

Epidural Lidocaine

In all patients the upper level of analgesia ranged between T7 and T10. Control mean arterial pressure (92 ± 3 mmHg) remained unchanged 15 and 25 min after epidural lidocaine (94 ± 4 and 90 ± 5 mmHg, respectively). After epidural anesthesia, five patients reported easier breathing during the CO\(_2\) rebreathing maneuver. Three patients reported a feeling of sedation.

Table 2 shows that after epidural administration of lidocaine resting \(\dot{V}E\), \(f\), VT, and PET\(_{CO_2}\) values did not change, whereas the slope \(\dot{V}E/PET\(_{CO_2}\) increased significantly from its control value at 15 and 25 min. The correlation between individual plasma lidocaine levels and the changes in the slope \(\dot{V}E/PET\(_{CO_2}\) was not significant (\(r = 0.09\)). Figure 2 shows, however, that by plotting the mean plasma lidocaine values observed at each set of measurements after both intravenous infusion and epidural administration against the simultaneous mean changes in the slope \(\dot{V}E/PET\(_{CO_2}\), both sets of data fall nearly on the same line.

Discussion

The two groups of subjects were not different with respect to age, sex ratio, height, and weight. In the epidural group, the values of the slope \(\dot{V}E/PET\(_{CO_2}\) were less than those of the intravenous lidocaine group.

However, this difference was not statistically significant. The mean value of the slope \(\dot{V}E/PET\(_{CO_2}\) in the epidural group was at the lower limit of the normal range for young adults, as reported by Irsigler.\(^5\) This is probably due to the broad range of individual values of the ventilatory responses to hypercapnia in normal humans. In addition, the subjects in the epidural group had a mean age that was slightly older than in Irsigler's study and it has been demonstrated that aging reduces the ventilatory responses to hypercapnia.\(^6\)

The results of this study confirm that intravenous lidocaine infusion induces a stimulation of the ventilatory response to CO\(_2\). The effect of intravenous lidocaine on the ventilatory response to CO\(_2\) already has been

![Fig. 1. Plasma lidocaine levels (\(\mu g/ml\)) are plotted against changes from control in the slope \(\dot{V}E/PET\(_{CO_2}\) (per cent). A positive correlation exists during and after intravenous infusion of lidocaine: \(r = 0.58\), \(n = 24\), \(P < 0.01\).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931407/ on 07/20/2018)
studied. Lidocone infusion in enflurane anesthetized dogs induces a decrease in the ventilatory response to CO₂. Other studies have been performed in awake humans. Camporese et al. observed no change in the slope VE/PETCO₂ 5 min after a loading dose of 100 mg/60 kg of lidocaine. Gross et al. reported recently that the method of lidocaine administration may affect the ventilatory response to CO₂, since a bolus dose was followed by a transitory decrease in the slope VE/PETCO₂, whereas a constant rate of infusion induced an increase in the slope VE/PETCO₂. Our results were consistent with these results. In addition, we found that the increase in the slope VE/PETCO₂ correlated with plasma lidocaine levels. Minute ventilation may be influenced by the mechanical properties of the respiratory system. However, in the absence of preexisting bronchospasm, intravenous infusion of lidocaine has never been reported to have bronchodilating properties. We can therefore presume that this lidocaine-induced ventilatory stimulation is probably the result of a stimulation of central inspiratory activity.

Epidural lidocaine was also responsible for a stimulation of the ventilatory response to CO₂. This effect may be related either to the systemic effect of the drug or to the consequences of the induced neural blockade. Epidural blockade may provoke a decrease in arterial pressure, which may induce a stimulation of ventilatory drive. Since in this study, arterial pressure remained constant, this possibility seems unlikely. The blockade of inhibitor peripheral afferents or a change in the geometry of the respiratory system during epidural blockade are other possibilities to account for the observed ventilatory stimulation. However, no data are available in favor of this hypothesis. Moreover, the effect of chest wall block alone, produced by spinal anesthesia, has already been studied by Eisele et al. Although only two patients were included in that study, no change in the slope VE/PETCO₂ was noted. We can therefore conclude that the ventilatory stimulation observed after epidural lidocaine probably results only from the systemic effects of the drug, as suggested by figure 2. The absence of correlation between individual plasma lidocaine levels and the changes in the slope VE/PETCO₂ during epidural anesthesia is probably due to a beta error (type II).

It was interesting to note that all the subjects in the intravenous group and three patients in the epidural group reported a sedative effect after lidocaine administration. This clinical effect was not associated with any ventilatory changes during resting ventilation. Indeed,
in both groups, during resting conditions, no change in the ventilatory variables was observed after lidocaine administration. This result confirms a previous study of Jorgfeldt et al. 10

In conclusion, epidural lidocaine induces an increase in slope of the ventilatory response to carbon dioxide, which results from the systemic effect of the drug.

The authors thank Drs. P. R. Bromage and A. Edouard for their valuable review of the manuscript, Mrs. M. J. Mayaux for the statistical advise, Miss M. Hriot for technical assistance, and Miss G. Rosine for secretarial assistance.

References