Respiratory Depression from Alkalosis and Opioid Interaction in Man

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Depression of respiration by alkalosis and opioid interaction in man was studied in a double-blind experiment utilizing changes in the ventilatory response to carbon dioxide. In each of two weekly sessions, control responses were determined before and after infusion of a liter of fluid which consisted of either saline solution as a placebo or 3.3 mEq/kg sodium bicarbonate. The bicarbonate infusion shifted the ventilatory response curve 6.2 torr to the right of, but parallel to, the ventilatory response curve after the saline placebo. Following each infusion, cumulative oxymorphone dose-response curves were obtained during isohypercapnia by observing the change in ventilation with each incremental intravenous dose. The two logarithmic dose-response curves were parallel. The total dose of 57 μg/kg oxymorphone shifted ventilatory response curves 19 and 16.3 torr to the right of the control response curves after bicarbonate and saline infusions, respectively. These shifts were not significantly different. Similarly, cumulative effects of nalozone given after oxymorphone were studied. A total of 57 μg/kg nalozone reversed 78 and 75 per cent of the oxymorphone depression in the two instances (significant reversal but insignificantly different comparing the results after the two different infusions). Respiratory depression produced by alkalosis and oxymorphone was thus additive. Nalozone effectively antagonized only the component of depression induced by oxymorphone, and modest changes in pH did not alter its action. (Key words: Ventilation; oxymorphone; Ventilation: alkalosis; Analgesics, narcotic: oxymorphone; Antagonists, narcotic: nalozone; Acid-base equilibrium: alkalosis.)

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THE RESPIRATORY EFFECTS of opioid therapy and those of alkalosis have been studied separately and reviewed in detail. Their interaction with regard to ventilatory control has never been carefully studied. Since both cause hypoventilation, there is a possible additional hazard in administration of opioid to patients with alkalosis. We report here a quantitative study of the interaction of the effects of acute metabolic alkalosis and oxymorphone on ventilatory control in awake man. The carbon dioxide-sensitive portion of respiratory control can be studied both by means of steady-state ventilatory response curves and by observation of ventilatory change during deliberately controlled isohypercapnia, utilizing the alveolar control concept of Lamberts. The combination of the two is a particularly powerful technique for analysis of the extent to which PCO₂ regulates breathing, for the stimulus is kept constant throughout. Therefore, changes in ventilation resulting from drug or pH effects are not diminished by concomitant changes in stimulus as well as response. Further changes in sensitivity, in this case represented by slope of the curve of the ventilatory responses to CO₂, can be allowed for. The results indicate simple addition of effects, with competitive antagonism of only the opioid-induced component by nalozone.

Methods

Eight healthy adult male volunteers (ages 21 to 27 years) participated in the experiment after informative interviews. Each subject was studied twice, with one week between studies to avoid cumulative effects. The protocols for the two weekly studies differed only in that an infusion of bicarbonate was received one week and an infusion of saline solution the other week. The order of the two infusions was varied among subjects.

The apparatus consisted of a nonrebreath-
ing circuit with mixing volumes just proximal to an inspiratory Sadd valve and just distal to an expiratory valve, a recording recycling spirometer,§ and analyzers for carbon dioxide and oxygen. The inspiratory limb of the breathing circuit had a volume of several liters and was open to the atmosphere at the beginning (similar to the input to the Emerson Respirator). Near the inspiratory valve was a small sidearm through which oxygen and carbon dioxide could be administered from compressed gas tanks via reducing valves and flowmeters. The mouthpiece for the subject was attached to a three-way valve between two Sadd valves so that the subject could be switched to the nonrebreathing circuit or alternately to a 1-liter rebreathing bag for determination of the mixed venous (rebreathing-oxygenated) Pco₂ by the technique of Collier.⁴

Carbon dioxide tensions of end-tidal and mixed expired gas were measured by an infrared analyzer calibrated with four known mixtures of carbon dioxide and oxygen and corrected for collision broadening due to nitrogen. A Paramagnetic oxygen analyzer continuously sampling at the mouthpiece was used to keep the oxygen concentration between 30 and 50 per cent. End-tidal carbon dioxide was considered to be the highest concentration recorded by the Capnograph, sampling at the rate of 500 ml/min from a catheter within a mouthpiece. The sampled gas was returned to the breathing circuit between the Sadd valves. End-tidal carbon dioxide was considered an accurate estimate of alveolar carbon-dioxide when the difference between mixed venous Pco₂ and end-tidal Pco₂ was less than 10 torr. Since there is a known difference between tensions in venous and arterial blood, averaging 7 torr, this assured us that our end-tidal sampling at rest did not include an A-a difference for carbon dioxide greater than 2 torr, and on the average it was considerably less. Further validation of the end-tidal technique was achieved by analysis of two arterial blood samples taken during the peaks of the carbon dioxide challenges before and after each infusion. Pco₂’s determined with the Severinghaus carbon dioxide electrode averaged less than 0.5 torr different from Capnograph-determined Pco₂’s, confirming the accuracy of the end-tidal measurements. This arterial blood was also analyzed for Po₂, pH, and sodium and potassium ion concentrations.

Steady-state estimates of the ventilatory responses to carbon dioxide were studied four times in each day’s study by adding pure carbon dioxide gas in measured quantities to the inspiratory limb. This procedure differed slightly from the conventional method, which employs constant increments of inspired carbon dioxide, typically 3, 5, and 7 per cent. With the modification used in the present study, the addition of 300, 600, and 900 ml of pure carbon dioxide sequentially, there is a slight decrease in the time between changing Pco₂ and reaching a new steady state. For example, when the subject is breathing approximately 6 l/min at rest and has 300 ml/min of CO₂ suddenly added to his inspirate, the inspirate is effectively 5 per cent carbon dioxide. This raises alveolar, arterial, and brain carbon dioxide tensions, stimulating ventilation. In a typical case, ventilation might increase to approximately 10 l/min, and as it increases, the effective inspired concentration of carbon dioxide would decrease to approximately 3 per cent. In effect, we give the subject a “loading dose” of carbon dioxide and progressively decrease it to the range we want to study. Ordinarily, with constant inspired carbon dioxide concentration, 6 to 10 minutes are allowed before ventilation becomes sufficiently stable validly to represent a “steady state.” We measured ventilation continuously and with our strategy found that it became sensibly stable only a minute or so sooner.

The ventilatory responses plotted in this report were taken from measurements made 8–10 minutes after changing the concentration of carbon dioxide inspired. The slope of the response, S, was derived from a least-squares regression of the three elevated carbon dioxide tensions, with one exception:

§ Wedge spirometer and recycler, Med-Science Corporation. §§.
§ Capnograph, Godart Company, §§.
### TABLE 1. Description of the Daily Protocol

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>Pretreatment phase&lt;br&gt;Application of monitoring instruments, start of slow iv drip of glucose in water&lt;br&gt;Acclimatization to the breathing circuit&lt;br&gt;Rebreathing mixed venous (oxygenated) carbon dioxide tension determined&lt;br&gt;Steady state response to carbon dioxide determined&lt;br&gt;Arterial sample drawn during stable ventilatory response to 900 ml/min of inspired carbon dioxide</td>
</tr>
<tr>
<td>Phase II</td>
<td>Infusion phase&lt;br&gt;One liter of saline or bicarbonate solution infused over 40 min&lt;br&gt;Steady-state ventilatory response to carbon dioxide re-determined&lt;br&gt;Arterial sample drawn at time of stable ventilatory response to 900 ml/min of carbon dioxide&lt;br&gt;Average end-tidal carbon dioxide tension noted for control during subsequent phase</td>
</tr>
<tr>
<td>Phase III</td>
<td>Opioid dose–response phase&lt;br&gt;Alveolar carbon dioxide tension maintained constant for 60 min&lt;br&gt;Five injections of oxymorphone given at 12-minute intervals&lt;br&gt;Steady-state ventilatory response to carbon dioxide re-determined&lt;br&gt;Unstimulated end-tidal carbon dioxide tension noted for Phase IV</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Opioid-reversal phase&lt;br&gt;Alveolar carbon dioxide tension maintained constant for next 36 minutes (except during episodes of emesis)&lt;br&gt;Three injections of naloxone given at 12-minute intervals&lt;br&gt;Steady-state ventilatory response to carbon dioxide re-determined</td>
</tr>
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Following the alkalotic oxymorphone study, we utilized the slope between the two highest points, i.e., with 600 and 900 ml/min of added carbon dioxide, since the responses were frankly curvilinear below that.

Twice during each study we utilized the alveolar control concept of Lambertsen² to study the incremental effects of injected oxymorphone or naloxone. One such period of control began after measurement of the response to 900 ml/min of carbon dioxide after infusion. By breath-by-breath monitoring of end-tidal Pco₂ and adjustment of the inspired carbon dioxide concentration we maintained Petco₂ constant within ± 1 torr. Similarly, after measurement of the post-oxymorphone ventilatory response to carbon dioxide, we maintained Petco₂ constant during incremental infusions of naloxone.

### Protocol

Each study consisted of four phases (table 1). In the pretreatment phase (I), infusion of 5 per cent glucose into a forearm was begun, electrocardiographic electrodes, precordial stethoscope, and a sphygmomanometer cuff were applied for monitoring vital signs, the subject acclimatized himself to the breathing circuit for 20 minutes. A "pretreatment" carbon dioxide response curve was then determined as described below.

The infusion phase (II) followed. The subject received either one liter of physiologic saline solution or one liter of water containing 3.3 mEq/kg of sodium bicarbonate over a 35-45-minute period. Each subject received both infusions on occasions a week apart, but the order was varied among subjects and not revealed to the observers. A post-
infusion carbon dioxide response curve was determined, completing the second phase.

The opioid dose–response phase (III) began immediately when stable ventilation at the highest concentration of carbon dioxide had been attained. $P_{\text{ET}}\text{CO}_2$ was noted at that point and kept constant during the infusion of oxymorphone. Five logarithmically graded doses of oxymorphone were given intravenously at 12-minute intervals without announcement and out of sight of the subject. The doses were chosen to produce a cumulative logarithmic progression, i.e., 9.5, 14.8, 23.1, 36.4, and finally 57 $\mu$g/kg. Ventilation in the last two to three minutes of the 12-minute intervals were tabulated to plot the response to oxymorphone. Because of the increasing depression, progressively less inspired carbon dioxide was needed to maintain $P_{\text{ACO}_2}$ constant. Twelve minutes after the final oxymorphone injection, we discontinued inspired carbon dioxide and began the observations for a determination of a steady-state ventilatory response curve. As before, this consisted of the administration of 0, 300, 600, and 900 ml/min of carbon dioxide for 10 minutes. This completed Phase III.

The opioid-reversal phase (IV) began with a 10-minute observation of unstimulated respiration. Average $P_{\text{ET}}\text{CO}_2$ in the last two minutes was noted and maintained during the subsequent infusions of naloxone except when interrupted by intervals of emesis. Naloxone was given three times at 12-minute intervals, for cumulative doses of 8, 25, and 57 $\mu$g/kg. Naloxone increased ventilation, necessitating increasing the concentration of inspired carbon dioxide. This phase ended

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**FIG. 1.** Steady-state ventilatory responses to carbon dioxide on the day of saline infusion. The solid line connects the points for the normal control response. After one liter of physiologic saline solution, infused intravenously, the responses were shifted left to the dashed line. Alveolar $\text{CO}_2$ was then controlled at about 55 torr and five logarithmically graded doses of oxymorphone given at 12-minute intervals. Ventilation 9 to 12 minutes after the five doses are indicated by the numbered points one through five. The heavy interrupted line is the steady-state response after oxymorphone, 57 $\mu$g/kg. Naloxone was given in three doses and the final steady-state response measured within 45 minutes (light interrupted line).
with determination of ventilatory responses to carbon dioxide by reduction of inspired carbon dioxide concentration to 600, then 300, and finally 0 ml/min at 10-minute intervals, plotting the stable ventilation in the last three minutes of each interval.

At the conclusion of Phase IV, the subjects were taken to the recovery room, where they remained for at least an hour. Each man returned 24 to 35 hours after the study, completed the symptom check list, and discussed any problems with the investigators.

### Table 2. Ventilatory Responses to Carbon Dioxide in Eight Subjects (Means ± SE)

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Respiratory Minute Volume (l/min)</th>
<th>End-tidal Carbon Dioxide Tension (torr)</th>
<th>Slope of Ventilatory Response Curve (l/min/torr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before saline</td>
<td>7.5 ± 0.7</td>
<td>43.2 ± 0.5</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>Before bicarbonate</td>
<td>7.9 ± 0.8</td>
<td>43.2 ± 1.0</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>8.9 ± 0.7</td>
<td>42.7 ± 0.6</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>7.9 ± 0.8</td>
<td>48.9 ± 1.2</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>6.9 ± 0.6</td>
<td>53.3 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>6.4 ± 0.7</td>
<td>60.1 ± 2.0</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>Phase IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>9.0 ± 0.7</td>
<td>41.9 ± 1.7</td>
<td>3.2 ± 1.8</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>8.9 ± 0.8</td>
<td>45.3 ± 1.8</td>
<td>2.6 ± 0.5</td>
</tr>
</tbody>
</table>
Results

The Pretreatment Phase

Mean values for the control ventilatory responses to carbon dioxide of the eight subjects are graphed as solid lines in figures 1 and 2. The mean slopes of the responses on the day of saline infusion and on the day of bicarbonate infusion were insignificantly different (table 2). Respiratory minute volumes at rest were normal and insignificantly different, and end-tidal carbon dioxide tensions averaged slightly more than 43 torr and were also insignificantly different. The Pco2's, which were at the high side of the normal range, are attributed to the combined effects of the increased apparatus deadspace (70 ml—associated with coupling of the low-resistance Sadd valves, the three-way tap, and the mouthpiece), the relaxed state of the subjects, who were accustomed to the apparatus and experiment, and slow respiratory frequencies, characteristically 9 to 11 per minute.

The Infusion Phase

During bicarbonate infusion, there were increases of approximately 15 per cent in both minute volume and PETCO2 associated with the increased carbon dioxide excretion load. None of the subjects was aware of this hyperventilation. Comparing the post-saline and post-bicarbonate results, we found both resting ventilation and displacement of the response to CO2 significantly different. The respiratory minute volume was 8.9 ± 0.7 l/min after saline solution and 7.9 ± 0.8 l/min after bicarbonate solution. A matched-pair t test showed that the probability that this difference could occur by chance was less than 5 per cent. Displacement of the ventilatory responses, calculated at a Ve of 20 l/min, showed that bicarbonate infusion caused a
rightward shift of 5.6 torr from the Phase I curve ($P = 0.003$), while the saline infusion shifted the ventilatory response 0.6 torr to the left of the Phase I control ($P > 0.1$). The difference between Phase II curves was $6.2 \pm 0.8$ torr.

Arterial $pH$, determined during challenge with 900 ml/min of inspired carbon dioxide, was $7.35 \pm 0.01$ (SEM) at $Paco_2$ 47.3 ± 2.1 torr after saline infusion. After bicarbonate infusion the $pH_a$ was $7.46 \pm 0.01$ at $Paco_2$ 53.2 ± 1.3 torr. Base excesses were $-0.3 \pm 0.8$ after saline and $12.3 \pm 0.7$ mEq/l after bicarbonate infusion. Since $pH_a$ values were measured at systematically different carbon dioxide tensions, the difference between them represents the combined effects of the metabolic alkalosis and a compensatory respiratory acidosis. Individual values were used to calculate a difference in $pH_a$ at a common $Pco_2$, which for the two studies was $0.15 \pm 0.01$ $pH$ units.

Although all measured electrolyte values were within normal ranges, serum potassium decreased significantly with bicarbonate infusion, averaging 0.5 mEq/l less than before treatment. Sodium increased 2.2 mEq/l during bicarbonate infusion (not significant). The changes from control in the saline-infusion day were an insignificant increase in potassium and an insignificant decrease in sodium.

THE OXYMORPHONE DOSE-RESPONSE PHASE

The five doses of oxymorphone were given while $Pco_2$ was controlled at 55 torr on the day of saline infusion and 60 torr on the day
of bicarbonate infusion. Respiratory minute volumes were 33.7 ± 4.0 and 33.0 ± 3.7 l/min (insignificantly different) on the two days, indicating that the difference in P_{ETCO2} reflected the metabolic alkalotic depression. The incremental injections of oxymorphone resulted in log linear decreases in ventilation on both days. The data are represented in figure 3, in which the average ventilation recorded 9 to 12 minutes post-drug is plotted against cumulative dose of oxymorphone. At no point is the difference between the bicarbonate and saline infusion data significantly different. The dose–response curves clearly have the same slope.

The post-opioid ventilatory response curves (heavy interrupted lines of figures 1 and 2) show an exaggeration of the initial “hockey-stick” deflection in the lower end-tidal CO₂ ranges, especially after bicarbonate infusion; however, the slopes are not significantly different from those of the control curves at the higher two end-tidal carbon dioxide tensions. The total dose of oxymorphone, 57 µg/kg, significantly shifted the ventilatory response curve 16.3 torr to the right of the post-saline infusion curve and 19.0 torr to the right of post-bicarbonate infusion curve. Although these are highly significant displacements, the difference between them, 2.7 torr, is not significant (P = 0.3).

THE OPIOID-REVERSAL PHASE

Just before naloxone injection, the relaxed, sedated subjects had a mean nonstimulated minute volumes of 6.3 l/min at P_{ETCO2}, 50.7 torr on the saline-infusion day and 6.3 l/min at P_{ETCO2}, 58.5 torr on the bicarbonate-infusion day. Except during emesis, P_{ETCO2} was maintained at these levels during naloxone infus. Within one to three minutes after initial injection of naloxone, dramatic arousal occurred. The subjects first wakened, then experienced marked dysphoria, followed by sweating, tachycardia, slight elevation of systolic blood pressure (mean increase 5 torr), diaphoresis, headache, and waves of nausea accompanied by vomiting which was severe enough to prevent continuous end-tidal CO₂ control and V̇E measurement in 12 of the 16 studies. This, in addition to voluntary hyperventilation in an attempt to control nausea (reported by subjects subsequently), suggest that the dose–response curves of figure 4 probably represent unsteady states with increased ventilation. Despite greater than normal ventilation 9 to 12 minutes after 57 µg/kg of naloxone, there is evidence that the oxymorphone depression was not completely reversed by naloxone. The steady-state ventilatory responses to carbon dioxide (light interrupted lines of figures 1 and 2) were still displaced to the right from the post-infusion responses. On the day of saline infusion oxymorphone had displaced the ventilatory response 16.3 torr and naloxone had shifted it back toward normal by 12.2 torr, representing 75 per cent reversal of the oxymorphone effect. On the day of bicarbonate infusion oxymorphone caused a 19.0 torr shift to the right, which was reversed by 14.7 torr (78 per cent reversal) after naloxone. The difference between these reversals is insignificant (P = 0.38).

SUBJECTS’ IMPRESSIONS

Subjects reported vascular burning sensations, chilliness, and inconstant uneasiness during the hypertonic bicarbonate infusion. These symptoms stopped on completion of the infusion and were not noted during saline infusion. One subject developed phlebitis in the forearm vein used for bicarbonate infusion and one subject complained of subsequent tenderness in the radial artery used for arterial sampling. No other symptom was associated with this phase of the study.

In the post-study interviews the subjects described the effects of oxymorphone administration as typical “rushes” lasting 30 to 40 seconds. The sensations of warmth, tingling, giddiness, euphoria, and increasing sedation were common to both the alkaloitic and the normal state. Peak depression was scored as 80 per cent (range 50 to 95 per cent, but not normally distributed) on a scale where 100 per cent was defined as unconscious.

For four to six hours afterwards, the subjects felt drowsy, cheerful, weak, and experienced impairment of concentration, symptoms of decreased gut and urinary tract motility, itchiness, waves of nausea and
vomiting, and sleepiness that persisted for 8–12 hours after the study.

Discussion

Our bicarbonate dose of 3.3 mEq/kg shifted the ventilatory response curve 5.6 torr to the right, while saline solution shifted it 0.6 torr to the left. The pH in blood drawn during CO₂ challenge was raised 0.11 units by the bicarbonate, which represents a 0.15 increase in pH resulting from the metabolic alkalosis and a 0.04 decrease in pH due to the compensatory respiratory acidosis. This change of 0.37 torr per 0.01 pH unit is in close agreement with the results of Katsaros and associates, who found a 0.4 torr shift to the right. The slight decrease in pH after saline infusion is attributable to dilutional acidosis. The constancy of slope of the ventilatory responses after bicarbonate has also been reported by Katsaros et al., by Stone, by Falchuk et al., and by Goldring et al., although not specifically reported. The last group also reported a dependence on serum potassium, which stimulated our measurement of serum electrolytes. Alkalosis associated with marked loss of potassium and no urinary hydrogen ion loss, achieved with thiazide and aldosterone, gave normal PCO₂’s and ventilation. We produced only mild hypokalemia from bicarbonate alkalosis and made measurements before urinary losses could become significant. We would, however, caution against extending our results to all states of chronic acid–base imbalance.

It is important to distinguish between acute and chronic alkalosis because of the uncertainty as to the exact locus and nature of stimulant action of the carbon dioxide–bicarbonate–hydrogen ion system. Lambertsen has shown that 45 per cent of the stimulatory effect of an acute increase in CO₂ can be eliminated by buffering the increase of hydrogen ion. This would imply that CO₂ has separable actions, one by virtue of CO₂ hydration and ionization which increases hydrogen ion concentration, and another by some molecular effect of carbon dioxide itself.

Dynamic consideration suggests an alter-
are minimized as CO₂ is increased, and are eventually abolished or swamped by the increase of ventilation associated with increasing carbon dioxide concentrations achieved during the response challenge. If this is so, our curvilinear CO₂ response curves after oxymorphone suggest that the opioid is less effective in depressing such non-CO₂-dependent stimuli to respiration than it is in depressing the ventilatory response to carbon dioxide directly.

Likewise, the naloxone reversal of depression was equally effective with alkalosis and with normal acid-base balance. The dose-response curves of oxymorphone and naloxone are those expected for a potent agonist and pure competitive antagonist. From the observation that the post-saline and post-bicarbonate dose-response curves for these two drugs overlay each other so closely, we further conclude that ventilatory depression resulting from alkalosis and ventilatory depression caused by opioids are additive, with no active interaction. The naloxone reversal of only the opioid effect implies that alkalosis and opioids affect dissimilar portions of the respiratory control system.

Metabolic alkalosis is an uncommon clinical entity, and acute alkalosis is even more rare except after vigorous bicarbonate therapy. Anesthetists are among the physicians most likely to encounter acute alkalotic hypoventilation. They are also among the most likely to employ other depressants such as opioids, and need to appreciate the possible interaction. In the present work it is shown that the two types of depressants are simply additive, unlike the interaction of sleep and opioid.¹²

The opioids for this study were supplied through the courtesy of Dr. Ralph Jacobsen of Endo Laboratories, Garden City, New York.

References