Interaction of the Effects of Naloxone and Oxymorphone on Human Respiration

Tamas Kallos, M.D.,* Howard E. Hudson, M.D.,† Jean-Claude Rouge, M.D.,‡ Theodore C. Smith, M.D.§

Naloxone (Narcam) administered to human volunteers in mixtures with oxymorphone reduced the respiratory depressant and sedative effects of the opioid. The 7.3-torr shift in CO\textsubscript{2} response curve from 15 mg/kg of oxymorphone was reduced by 66 percent when naloxone, 14 mg/kg, was administered simultaneously. The ability of naloxone to antagonize mild degrees of respiratory depression is in contrast to the ineffectiveness of nalorphine and levallophan against similar degrees of opioid depression and may be attributed to its lack of intrinsic depressant properties. (Key words: Naloxone; Opioid antagonists; Respiratory effects of opioids and antagonists.)

While nalorphine and levallophan are effective antagonists of severe opioid depression, their ineffectiveness against mild degrees of depression has been puzzling. Bellville and Fleischli have explained this phenomenon based on Arien's theory of competitive dualism. Keats and Telford have found a ceiling to the agonistic effects of nalorphine. Based on these data, the apparent discrepancy may be explained: nalorphine administered after severe opioid depression will displace the opioid molecules and substitute its limited depression for the more severe opioid depression. When it is given to a mildly narcotized person (with depression less than the ceiling agonistic effect of nalorphine) it will augment the depression up to its own ceiling effect. This convergence of interaction toward the intrinsic agonistic effect of the "antagonist" has been demonstrated by Bellville and Fleischli for morphine and nalorphine and by Rouge and Smith for meperidine and levallorphan. It would be further evidence for the theory of competitive dualism if "antagonists" with either greater or less intrinsic agonistic activity were shown to fit the proposal.

Naloxone (N-allyl-noroxymorphone) is an antagonist without depressing properties. We studied the interaction of premixed naloxone and oxymorphone given intramuscularly. Despite suboptimal selection of dosage ratios, due to an overestimate of the potency of naloxone and an error in the assay of drugs supplied for this investigation, we demonstrated a dose-related reversal of mild to moderate narcotic depression, in contrast to the effects of nalorphine and levallophan. These results fit the theory of competitive dualism in the limiting case of absent agonistic activity, i.e., pure competitive antagonism.

Methods

Two similar studies were executed. In the first, the effective dose of naloxone was selected from published recommendations. When analysis showed that the dose range being used was inadequate, we undertook a second, similar, study, utilizing larger doses.

Study I

Five combinations of oxymorphone and naloxone were tested in a double-blind protocol involving ten subjects, each of whom returned in five consecutive weeks for study. The doses

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Naloxone was kindly supplied by Dr. Ralph Jacobsen of Edele Laboratories, Garden City, New York, in vials of nominal content 0.4 mg/ml. Subsequent bioassay of this lot of vials showed a content only 65 percent of nominal. Later lots were produced with a somewhat different synthesis, and were fully potent.
of oxymorphone (table 1) were chosen to represent a normal postoperative analgesic dose, 14 μg/kg, and half and twice that much.11,12 The doses of naloxone were intended to represent an efficacious dose, as suggested by Foldes et al.13 and by Sadove et al.,14 and half and twice that dose. Subsequent assay of the batch of naloxone showed that it contained only 65 per cent of the labeled amount, so that the doses actually employed were 1.6, 3.3, and 6.6 μg/kg. The order of studies for any one subject was chosen randomly from a 5 × 5 Latin-square design, duplicating each cell.15 Double-blind conditions were maintained until analysis of the records had been completed. The seven male and three female subjects ranged in age from 21 to 37 years. Every subject was studied at least four hours postpartum in each of the five consecutive weeks. In preliminary studies, six of the ten subjects received 14 μg/kg oxymorphone alone in a single-blind protocol, and were observed with the same tests used in the double-blind trials. Two further subjects received 40 μg/kg of naloxone intravenously and the respiratory effects were studied by the method of rebreathing CO₂.

The respiratory apparatus, previously described,16 included a 9-liter Collins recording spirometer with a Reichert ventilometer to measure ventilatory volumes, a carbon dioxide

<table>
<thead>
<tr>
<th>Dose of Naloxone</th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.6 μg/kg</td>
<td>3.3 μg/kg</td>
</tr>
<tr>
<td>Dose of Oxymorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 μg/kg</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>14 μg/kg</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>7 μg/kg</td>
<td>X</td>
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</tr>
</tbody>
</table>

Table 2A. Effects of Different Mixtures of Oxymorphone and Naloxone on Resting Ventilation of Ten Subjects (Study I)*

<table>
<thead>
<tr>
<th>Minute volume (I/min)</th>
<th>Oxy. 7 μg/kg</th>
<th>Oxy. 14 μg/kg</th>
<th>Oxy. 21 μg/kg</th>
<th>Oxy. 28 μg/kg</th>
<th>Nalox. 0 μg/kg</th>
<th>Nalox. 3 μg/kg</th>
<th>Nalox. 6 μg/kg</th>
<th>Nalox. 12 μg/kg</th>
<th>Nalox. 24 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (I)</td>
<td>0.58 ± 0.41</td>
<td>0.60 ± 0.25</td>
<td>0.67 ± 0.27</td>
<td>0.29 ± 0.03</td>
<td>0.19 ± 0.03</td>
<td>0.09 ± 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar ventilation (I/min)</td>
<td>4.67 ± 0.30</td>
<td>3.87 ± 0.26</td>
<td>3.87 ± 0.26</td>
<td>3.50 ± 0.14</td>
<td>3.87 ± 0.14</td>
<td>3.87 ± 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-tidal CO₂ tension (torr)</td>
<td>41.8 ± 0.75</td>
<td>41.4 ± 0.70</td>
<td>41.4 ± 0.70</td>
<td>45.2 ± 0.56</td>
<td>45.2 ± 0.56</td>
<td>46.2 ± 0.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed venous CO₂ tension (torr)</td>
<td>49.8 ± 1.00</td>
<td>52.9 ± 0.83</td>
<td>52.9 ± 0.83</td>
<td>54.1 ± 1.32</td>
<td>54.1 ± 1.32</td>
<td>54.1 ± 0.97</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean values ± SE.
† Significantly different from control and, in case of largest and smallest oxymorphone doses only, from each other.
‡ Significantly different from control (P < 0.05) but not from each other.

Table 2B. Effects of Different Mixtures of Oxymorphone and Naloxone on Resting Ventilation of Ten Subjects (Study II)*

<table>
<thead>
<tr>
<th>Minute volume (I/min)</th>
<th>Oxy. 0 μg/kg</th>
<th>Oxy. 14 μg/kg</th>
<th>Oxy. 21 μg/kg</th>
<th>Oxy. 28 μg/kg</th>
<th>Nalox. 0 μg/kg</th>
<th>Nalox. 3 μg/kg</th>
<th>Nalox. 6 μg/kg</th>
<th>Nalox. 12 μg/kg</th>
<th>Nalox. 24 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (I)</td>
<td>7.64 ± 0.40</td>
<td>6.91 ± 0.35</td>
<td>7.16 ± 0.41</td>
<td>8.04 ± 0.42</td>
<td>6.50 ± 0.03</td>
<td>6.50 ± 0.03</td>
<td>6.50 ± 0.03</td>
<td>6.50 ± 0.03</td>
<td>6.50 ± 0.03</td>
</tr>
<tr>
<td>Alveolar ventilation (I/min)</td>
<td>4.80 ± 0.32</td>
<td>4.34 ± 0.29</td>
<td>4.78 ± 0.34</td>
<td>4.13 ± 0.39</td>
<td>4.78 ± 0.34</td>
<td>4.78 ± 0.34</td>
<td>4.78 ± 0.34</td>
<td>4.78 ± 0.34</td>
<td>4.78 ± 0.34</td>
</tr>
<tr>
<td>End-tidal CO₂ tension (torr)</td>
<td>44.3 ± 0.7</td>
<td>44.6 ± 1.0</td>
<td>44.3 ± 0.72</td>
<td>45.5 ± 0.93</td>
<td>44.6 ± 1.0</td>
<td>44.6 ± 1.0</td>
<td>44.6 ± 1.0</td>
<td>44.6 ± 1.0</td>
<td>44.6 ± 1.0</td>
</tr>
<tr>
<td>Mixed venous CO₂ tension (torr)</td>
<td>56.1 ± 2.78</td>
<td>—</td>
<td>53.8 ± 1.34</td>
<td>—</td>
<td>53.8 ± 1.34</td>
<td>53.8 ± 1.34</td>
<td>53.8 ± 1.34</td>
<td>53.8 ± 1.34</td>
<td>53.8 ± 1.34</td>
</tr>
</tbody>
</table>

* Mean values ± SE.
† Significantly different from control (P < 0.05).
absorber, a Godart NV capnograph to measure carbon dioxide tension, and a Beckman C2 paramagnetic analyzer to check inspired oxygen concentrations.

The subjects rested for a half hour in the semirecumbent position prior to the intramuscular injection. After another half hour they began breathing into the spirometer circuit. Ventilatory measurements, made between 40 and 70 minutes after the injection, consisted of: minute ventilation (VE); respiratory rate (f); end-tidal (PETCO2), mixed expired (PECO2), and mixed venous (oxygenated)17 (PVCO2) carbon dioxide tensions; oxygen consumption (VO2); and the spirometric lung volumes, including vital capacity, inspiratory capacity, expiratory reserve volume, and forced expiratory volumes (FEV1, FEV2). From these data, tidal volume (Vt), alveolar ventilation (VA), anatomic deadspace, CO2 excretion (VCO2), and respiratory quotient (RQ) were calculated. The exclusion of the carbon dioxide absorber permitted accumulation of carbon dioxide at a rate between 1 and 1.5 torr/min, which was continued until PETCO2 had increased by 15 torr or VE had reached 20 l/min, whichever took longer.

Control measurements were made after a half hour of rest during the first and last study session, preceding the injections, and averaged. Previous studies have shown that values for placebo effects and control values are indistinguishable except for VO2 and VCO2.16 Individual ventilatory responses to carbon dioxide were plotted from the average VE and PETCO2 every 30 seconds during rebreathing. PETCO2 values at 10, 15, and 20 l/min VE were interpolated from the individual ventilatory response graphs and averaged. The slopes of the curves were calculated between 10 and 20 l/min ventilation. The displacements of the curves from the control were obtained by averaging the changes in PETCO2 at 10, 15, and 20 l/min VE, thus avoiding the assumption of parallel-straight-line responses and minimizing the variation due to choice of a single ventilatory level.

STUDY II

After the problem with dosage had been uncovered, ten additional subjects of the same age range, all males, received intramuscularly oxymorphone, 14 µg/kg, mixed with either 14 or 28 µg/kg naloxone, in a similar double-blind study of CO2 responsiveness, but without the ancillary pulmonary function tests described above. Each subject returned one or two weeks after the first session for the second one. The measurements included resting ventilation, deadspace, gas exchange, and ventilatory response to CO2, determined with a steady-state technique previously described.18

Within 24 hours after each session of both studies, the volunteers completed a questionnaire for the assessment of the subjective effects of the mixtures. Sedation was graded from 0 (no noticeable effect) to 10 (“out cold”).

Tests of statistical significance employed analysis of variance and the studentized range statistic14,19 if the F ratio exceeded that for a 5 per cent probability.

Results

In Study I each drug combination produced statistically significant respiratory depression, as indicated by dose-related decreases in resting minute ventilation, tidal volume, and alveolar ventilation, and increases in end-tidal and mixed venous carbon dioxide tensions (table 2A). Spirometric lung volumes were not changed by these drugs, and the anatomic deadspace changes were not dose-related.

Oxygen consumption was 0.245 ± 0.011 l/min, within the predicted basal limits, before the drugs, and decreased slightly after administration of the drug combinations in a non-dose-related fashion. Carbon dioxide excretion after each drug combination was significantly below the control values, suggesting that a new steady state had not been attained, and the CO2 tensions are slightly underestimated in the unstimulated state. RQ did not change significantly.

The data for ventilatory responses to carbon dioxide from Study I are presented in table 3A and figure 1. With ventilation of 10 l/min or more, the curves were linear, and they shifted to the right of control after each administration of each drug combination, indicating respiratory depression. Failure to reach a steady state for CO2 exchange, with Fr CO2 slowly increasing, partially accounts for the “hockey stick” lower segment of the CO2 response.
### Table 3A. Effects of Different Mixtures of Oxymorphone and Naloxone on the Ventilatory Responses to Carbon Dioxide of Ten Subjects (Study I)

<table>
<thead>
<tr>
<th>PrCO₂* at Vₖ = 20 l/min (torr)</th>
<th>Oxy. 0 Nal. 0</th>
<th>Oxy. 14 µg/kg Nal. 0.5 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 0.5 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 1.0 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 3.5 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 1.0 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 3.5 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope between 10 and 20 l/min</td>
<td>1.58</td>
<td>1.53</td>
<td>1.53</td>
<td>1.53</td>
<td>1.47</td>
<td>1.39</td>
<td>1.39</td>
</tr>
<tr>
<td>Mean shift of responses (torr)</td>
<td>7.3</td>
<td>4.5</td>
<td>5.6</td>
<td>6.7</td>
<td>7.5</td>
<td>8.2</td>
<td>8.2</td>
</tr>
</tbody>
</table>

* Values for PrCO₂* mean ± SE.
† Six subjects. These data are not part of the randomized double-blind series.
‡ Significantly different from control (P < 0.05).

### Table 3B. Effects of Different Mixtures of Oxymorphone and Naloxone on the Ventilatory Responses to Carbon Dioxide of Ten Subjects (Study II)

<table>
<thead>
<tr>
<th>PrCO₂* at Vₖ = 20 l/min (torr)</th>
<th>Oxy. 0 Nal. 0</th>
<th>Oxy. 14 µg/kg Nal. 0.5 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 0.5 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 1.0 µg/kg</th>
<th>Oxy. 14 µg/kg Nal. 3.5 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope between 10 and 20 l/min</td>
<td>2.0</td>
<td>2.3</td>
<td>3.0</td>
<td>2.7</td>
<td>2.65</td>
</tr>
<tr>
<td>Mean shift of responses (torr)</td>
<td>2.43</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* Values for PrCO₂* mean ± SE.
† Significantly different from control (P < 0.05).
Fig. 1. Ventilatory responses to CO₂ accumulation during rebreathing, before and 50 to 70 minutes after intramuscular injection of mixtures of oxymorphone and naloxone. Each of ten individual response curves for PetCO₂ was interpolated at 10, 15, 20, and 25 l/min and the results were averaged for each drug mixture. All mixtures were depressing. There were, however, a significant dose-related decrease in depression with increasing naloxone dose and an increasing depression dose-related to oxymorphone with a constant naloxone dose.

A constant dose of naloxone, and for naloxone (P < 0.05) in the presence of a constant dose of oxymorphone. Oxymorphone (14 μg/kg) alone displaces the CO₂ response curve to the right by 7.3 torr. The largest dose of naloxone, 6.6 μg/kg, resulted in reduction of this depression by approximately 25 per cent.

Study II extended the naloxone dose range to 28 μg/kg. This caused additional antagonism of the oxymorphone effect, resulting in only small changes in resting Vₑ and PetCO₂ (table 2b) and lesser displacement of the response curves (fig. 2). The antagonistic effects of 14 and 28 μg/kg naloxone against 14 μg/kg of oxymorphone were not significantly different from each other (table 3b, fig. 2) (paired t test at Vₑ = 20 l/min), but both were significantly greater than those of 3.3 and 6.6 μg/kg naloxone (table 3a, fig. 1) (nonpaired t test).

The most common symptoms reported were drowsiness, dizziness, weakness, irritability, nausea, and vomiting. The subjects could discriminate among the drugs by the degree of symptoms, as well as the duration of effects.

Sedation (fig. 3) increased with increasing doses of oxymorphone in the presence of a constant dose of the antagonist, and lessened with increasing doses of naloxone in the presence of a constant dose of opioid. Twenty-eight micrograms per kilogram of oxymorphone with 3.3 μg/kg of naloxone were no more sedating than 14 μg/kg of oxymorphone alone. Similar relationships were observed for duration of effects: the maximum effect of 14 μg/kg of oxymorphone alone, on the average, lasted 4.1 hours, and its effects were noticeable for 6.7 hours. Increasing doses of naloxone shortened the duration of maximum effect and also the duration of noticeable effects.

Discussion

This study was deliberately similar to that of Rouge et al., who found that addition of doses of levallorphan from 10 to 40 μg/kg neither antagonized nor enhanced moderate respiratory depression produced by 1.65 μg/kg meperidine. They found a dose-related increase of sedation and respiratory depression when increasing doses of levallorphan were
Fig. 2. Steady-state ventilatory responses to CO₂ during Study II, before and after intramuscular injection of oxymorphone, 14 μg/kg, mixed with naloxone, either 14 μg/kg (circles) or 28 μg/kg (triangles). The effect of 14 μg/kg oxymorphone alone is also plotted (square symbols), although the data came from six other subjects, utilizing the rebreathing test of Study I.

combined with a constant dose of meperidine. In contrast, we found that naloxone antagonized even moderate degrees of narcotic sedation, as well as respiratory depression. The doses of naloxone initially chosen proved insufficient for complete reversal.

The discordant estimate of an effective antagonistic dose in prior studies can be explained by the experimental methods and designs. Foldes, using anesthetized subjects, produced stable respiratory depression by opioids and measured the transient increase in ventilation following intravenous administration of an antagonist. For illustration, assume that the control curve of figure 1 represents the condition before administration of

Fig. 3. Subjective assessment of depression by oxymorphone-naloxone mixtures. Naloxone significantly antagonized sedation.

<table>
<thead>
<tr>
<th>Oxymorphone (μg/kg)</th>
<th>Naloxone (μg/kg)</th>
<th>Degree of Sedation (Subjective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>28</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>6.6</td>
<td>0</td>
</tr>
</tbody>
</table>

Average of 10 trained subjects ± Standard Error
the opioid, and the curves of solid dots, after administration of the opioid. Assume that an antagonist capable of 50 per cent reversal is next given intravenously. Within a circulation time, the brain’s responsiveness is improved, and the appropriate response curve is now halfway between the control and drugged curves. In figure 1 the curve of open square symbols is a good approximation of such a case. In the brief period, arterial CO\textsubscript{2} tension in the brain will not change, but with the new responsiveness it elicits an increase of ventilation from less than 5 l/min to 8 l/min at 47 torr. As this is greater than the control ventilation of 7.5 l/min, the depression is adjudged completely reversed. Soon, however, the increased CO\textsubscript{2} excretion lowers body CO\textsubscript{2} stores (at a rate approximated by a first-order reaction with time constant of 15 to 20 minutes\textsuperscript{28}), and ventilation slowly decreases to 6.25 l/min. This is the steady state for half-reversal. But if ventilatory volume alone were used to judge depression, it would appear that the antagonist had a short duration of action. Thus, ventilatory measurements alone after IV doses underestimate both the dose for complete reversal and the duration of antagonistic effect.

As naltrexone has no significant agonistic effects, it should reverse mild as well as severe depression. Previously, Bellville and Fleischli\textsuperscript{6} and Rouge \textit{et al.}\textsuperscript{7} had shown that mild depression following opioids (i.e., below or at the ceiling of antagonist depression) was increased or not changed by increasing nalorphine or levallorphan dosages. Figure 4 summarizes our present data in a manner similar to that chosen by Bellville and Fleischli and Rouge \textit{et al.} Solid dots represent the major double-blind study (Study I), open circles the additional studies of oxymorphone alone and of oxymorphone plus increased naltrexone (Study II). The triangle represents two open trials of naltrexone alone, confirming the lack of respiratory depression by naltrexone reported by Jasinski.\textsuperscript{10} Lines were sketched by eye.

The unfortunate coincidence of a subpotent drug preparation and prior overestimates of naltrexone’s efficacy led us to study the lower dose–response range of naltrexone. The oxymorphone-produced depression was less than Rouge’s meperidine-induced depression, in the range where nalorphine and levallorphan clearly would add to opioid effect. Yet clear antagonism of both respiratory and sedative effects
was obtained. This is consistent with pure competitive antagonism, the extreme case of competitive dualism with absent agonistic effect. We are, therefore, led to predict that naloxone will reverse the moderate depression produced by opioid antagonists alone. Preliminary work has in fact shown this for the narcotic antagonist compounds cyclazocine, pentazocine, and levallorphan. If receptors for agonistic and antagonistic activity differ (receptor dualism), the finding of antagonism of antagonist by antagonist would require postulates of still additional receptors. Ocean's razor thus favors competitive dualism over receptor dualism (or "receptor polymy.").

The dose of naloxone necessary for half-reversal of the respiratory depression caused by 14 μg/kg of oxymorphone may be estimated from figure 4. This dose of oxymorphone produced a shift of about 7 torr in the CO2 response curve. Following the dotted dose-response line the dose of naloxone at half-reversal is in the range of 10 to 12 μg/kg.

Naloxone offers advantages over opioid antagonists in current use. It not only reduces respiratory depression and sedation but, having no agonistic action, would cause no harm when given to patients depressed by other drugs.

References

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