Specific and Nonspecific Antagonism of Morphine-Induced Respiratory Depression

C. N. Papadopoulos, M.D., and Arthur S. Keats, M.D.

Numerous investigators have noted that the dose of previously administered narcotic is a major factor in determining the degree of antagonism observed after nalorphine or levallorphan. Following a large narcotic dose, a small dose of narcotic antagonist consistently produces complete or even more than complete antagonism of almost all narcotic actions. In contrast, a narcotic antagonist administered after a therapeutic dose of narcotic (less than 15 mg./70 kg. of morphine or its equivalent) produces only partial, transient or no antagonism. Despite published case reports of dramatic antagonism by nalorphine in patients excessively depressed by therapeutic narcotic doses, a study of a group of such patients indicated that this was not a consistent response and antagonism frequently did not occur. Our clinical experience in antagonizing therapeutic doses of narcotics with nalorphine has been similarly inconsistent.

Since excessive depression from therapeutic doses of narcotics is not rare in clinical anesthesia, the present study was undertaken to provide a basis for rational therapy. A comparison was made of the efficacy of a specific narcotic antagonist (one which antagonizes the effects of narcotics only) and a nonspecific antagonist (one which antagonizes the central nervous system depressant effects of all drugs) in antagonizing the depressant effects of a therapeutic dose of morphine. Nalorphine was selected as the specific antagonist, methylphenidate as the nonspecific. In addition to antagonism of respiratory depression, the effect of these antagonists on oxygen uptake and the subjective effects associated with the two types of antagonism were also recorded.

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Methods

Six healthy males 22-27 years of age were subjects of this study (mean weight 74.1 ± 2.8 kg. and mean body area 1.68 ± 0.23 m²). Although designed as a complete crossover study, two subjects failed to complete the four drug sequences planned, and in one subject on one test day only data on oxygen uptake were obtained. The sequences consisted of the administration of one of four “agonists” following 10 mg. of morphine on four different test days. The four “agonists” were: (1) placebo (normal saline) (2) nalorphine 7 mg. (3) methylphenidate 10 mg. (4) methylphenidate 30 mg. These doses were not adjusted to body size, and all were given intravenously over a 2 minute period. The order in which the antagonists were administered to each subject was randomized, and 4 to 25 days separated successive tests in each subject. In addition to the sequences, 3 of the 6 subjects were given 30 mg. of methylphenidate intravenously without previous morphine on a separate occasion, and the effects measured one and three hours after administration. On the day of study each subject rested for 30 minutes and was then connected to the respiratory apparatus. After a period of 10 minutes for accommodation, control measurements were made. Morphine was given immediately following control measurements and its effects measured 60 minutes later. The antagonist was injected immediately after measurement of morphine effects, and antagonist effects were determined 30 minutes later. Therefore, morphine effects were measured 60 to 90 minutes after administration and antagonist effects 120 to 150 minutes after morphine.

At each measurement period oxygen uptake was first determined by allowing subjects to breathe room air through a mouthpiece at-
attached to a nonrebreathing valve and collecting expired air in a 60 liter Douglas bag for 5 minutes. The volume of air in the Douglas bag was measured with a dry gas meter and its oxygen concentration by a Beckman Model C oxygen analyzer. Oxygen uptake per minute was calculated from these values.

Respiratory depression was then measured in terms of the displacement of each subject's alveolar carbon dioxide tension-alveolar ventilation (P\textsubscript{ACO\textsubscript{2}} - \textit{VA}) curve produced by the drug when compared to the control curve. To obtain the P\textsubscript{ACO\textsubscript{2}} - \textit{VA} curves, subjects breathed gas mixtures which approximated 2, 4, and 6 per cent CO\textsubscript{2} through the mouth piece nonrebreathing valve assembly (dead space of 35 ml.). Expired gases were passed through a low resistance dry gas meter to measure minute volume which was then corrected to 37\degree C. Alveolar air was sampled continuously by a Rahn end-tidal alveolar air sampler and passed through an infrared carbon dioxide analyzer. Each subject breathed each gas mixture for 4 minutes to obtain maximum response before data were collected. Minute volume, respiratory rate and P\textsubscript{ACO\textsubscript{2}} were determined during two 2 minute periods on each gas mixture. From the mean values of these two periods alveolar ventilation was calculated assuming a dead space of 150 ml. per respiration. The data of each subject were then plotted as a respiratory stimulus-response (P\textsubscript{ACO\textsubscript{2}} - \textit{VA}) curve. The slope of the control curve for each subject was calculated and applied to the two postdrug curves. The displacement in mm. of mercury P\textsubscript{ACO\textsubscript{2}} of the postdrug from the control curve was determined for each subject. A displacement to the right represented a single expression for the respiratory depression produced by the drug and a displacement to the left represented respiratory stimulation. Statistical comparisons of mean values were made by the \textit{t}-test for paired replicates when possible or when unpaired by the \textit{t}-test for group means.

To estimate the subjective effects of each drug, subjects were asked nonspecific questions such as "How do you feel?" before each measurement period and their responses were recorded.

**Results**

Respiratory Depression of Morphine: The mean displacement of the P\textsubscript{ACO\textsubscript{2}} - \textit{VA} curve in 6 subjects (18 trials) by intravenous morphine was 6.44 ± 0.48 mm. of mercury. This displacement is notably less than the 10–12 mm. of mercury we have previously observed 60 minutes after a similar intramuscular dose of morphine in similar subjects.\textsuperscript{5,7} The difference may be due to our measurement of intramuscular effects at the time of peak action in contrast to measurement of intravenous effects during waning drug action. It is also possible that when given intravenously, a larger proportion of administered morphine goes to sites of detoxification rather than to sites of primary action, producing a more rapid decline in the time-effect curve compared to the intramuscular route.

Antagonism of Respiratory Depression by Nalorphine: Because of our previous difficulty in antagonizing therapeutic doses of morphine with nalorphine,\textsuperscript{8} a preliminary study was carried out to determine a dose of nalorphine and morphine which would consistently produce some antagonism when given at the time intervals selected for study. Trials were made of 25 mg. of morphine followed by 10 mg. of nalorphine and 10 mg. of morphine followed by 1, 3, 5, 7 and 10 mg. of nalorphine. From this nonsystematic study, it appeared that consistent antagonism of morphine respiratory depression could be achieved by 7 mg. of nalorphine. The respiratory stimulation following this dose of nalorphine is shown in figure 1, where the mean data of 4 subjects have been plotted. The mean displacement calculated from individual displacements is presented in table 1. Antagonism was not complete and respiration remained slightly depressed following nalorphine.

In contrast to nalorphine, the placebo produced additional respiratory depression suggesting a learned response in our subjects who were studied repeatedly. However, it is equally possible that the additional depression was secondary to the morphine sedation and inactivity required by the conditions of study.\textsuperscript{9} The additional placebo depression is similar in magnitude to that which followed
In the 3 subjects given 30 mg. of methylphenidate without previous morphine, the mean displacement of the $P_{CO_2} - V_A$ curve was $+2.7 \pm 1.0$ mm. of mercury $P_{CO_2}$ at one hour and $-1.0 \pm 1.1$ mm. of mercury at 3 hours. These displacements are similar to those cited above following an intramuscular placebo (3.3 mm. of mercury at one hour and 0.7 mm. at 3 hours). Surprising, the displacement was in the direction of respiratory depression not stimulation despite an increase in oxygen uptake (see below).

Changes in Oxygen Uptake: Oxygen uptake following morphine was measured 19 times in 6 subjects. In these 19 trials, the mean control oxygen uptake was $289 \pm 10.0$ ml/minute and decreased to $264 \pm 10.3$ ml/minute one hour after morphine ($P < 0.05$). This 7.4 per cent decrease in oxygen uptake is consistent with values reported by others following a therapeutic dose of morphine. In contrast, 30 mg. of methylphenidate, in the 3 subjects who did not receive morphine, increased oxygen uptake from a control of $255 \pm 18.8$ ml/minute to $313 \pm 19.7$ ml/minute at one hour and $316 \pm 25.8$ ml/minute at 3 hours. Because of the small number of subjects, the difference from control is significant ($P < 0.05$) only when pooled postdrug data are compared to controls.

The mean changes in oxygen uptake associated with antagonism are presented in table 2. Despite stimulation of respiration and unlike methylphenidate nalorphine did not increase oxygen uptake. Although the increase in uptake following 10 mg. methylphenidate was not statistically significant, the

| TABLE 1. Mean Displacements of Respiratory Stimulus Response ($P_{CO_2} - V_A$) Curves from Control Curves in Six Subjects Following Morphine and Morphine Antagonists (in mm. Hg $P_{CO_2}$ ± Standard Error of Mean) |

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Displacement by Morphine, 10 mg.</th>
<th>Antagonist</th>
<th>Displacement after Antagonist</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.3 ± 0.6</td>
<td>Saline (Placebo)</td>
<td>8.1 ± 0.95</td>
<td>+1.76 ± 0.41*</td>
</tr>
<tr>
<td>4</td>
<td>6.9 ± 1.5</td>
<td>Nalorphine, 7 mg.</td>
<td>2.5 ± 0.80</td>
<td>-4.35 ± 1.0*</td>
</tr>
<tr>
<td>4</td>
<td>5.3 ± 1.0</td>
<td>Methylphenidate, 10 mg.</td>
<td>3.5 ± 1.2</td>
<td>-1.87 ± 0.41*</td>
</tr>
<tr>
<td>5</td>
<td>7.1 ± 1.1</td>
<td>Methylphenidate, 30 mg.</td>
<td>3.4 ± 0.56</td>
<td>-3.70 ± 1.1*</td>
</tr>
</tbody>
</table>

* Significant difference at $P < 0.05$ by $t$-test for paired replicates.

Displacements were measured one hour after intravenous morphine and 30 minutes after the intravenous antagonist. Positive displacements represent respiratory depression; negative displacements represent respiratory stimulation.

ANTAGONISM OF MORPHINE INDUCED RESPIRATORY DEPRESSION BY NALORPHINE

an intramuscular placebo in similar subjects without morphine. Antagonism of Respiratory Depression by Methylphenidate: Ten milligrams of methylphenidate produced a slight, but significant stimulation of respiration which was less than the stimulation of 30 mg. methylphenidate (table 1). As with nalorphine, the respiratory stimulation of 30 mg. of methylphenidate did not return the stimulus-response curve to control level and respiration remained slightly depressed (fig. 2).

FIG. 1. Displacement of respiratory stimulus-response curve by morphine followed by nalorphine. Mean values of 4 subjects. Displacement of the curve to the right represents respiratory depression, to the left respiratory stimulation.
trend was present and the increase following 30 mg. of methylenedidate was significant (P < 0.05).

Subjective Effects Associated with Antagonism: There was a striking difference in the subjective effects reported by the subjects following the two types of antagonists. All 4 subjects who subsequently received nalorphine reported only that they were either sleepy or sedated after morphine. After the administration of nalorphine, all 4 continued to be sleepy and 2 were visibly sedated. Two were dizzy, one had difficulty focusing eyes and one complained of nausea. Two of the 4 reported an inability to control their thoughts. All 6 subjects who subsequently received 30 mg. of methylenedidate reported that they were sleepy after morphine, and 2 complained of itching. After methylenedidate, 5 of the 6 reported that they were more alert and awake. The other did not feel more awake but became restless, talkative and complained of difficulty in focusing his eyes and in concentrating. Of the 5 who were more alert, 3 felt stimulated, energetic and displayed tremor of the hands. Two were restless, two had difficulty focusing eyes, and one had difficulty in concentrating. Nervousness, nausea and difficulty controlling thoughts were each reported once. The subjects who received methylenedidate appeared stimulated and two stated, "There is so much I have to do," "I feel like a million dollars."

Discussion

Excessive central nervous system depression induced by drugs (excessive sedation, respiratory depression and hypotension) not infrequently follows preanesthetic medication and is not rare in the postanesthetic recovery room. In both clinical situations the depression is usually the result of more than one drug, most commonly a combination of narcotic, barbiturate, phenothiazine, scopolamine and an inhalation anesthetic. In such a "mixed" depression, it is tempting to administer a specific narcotic antagonist in the hope of eliminating that portion of the general depression produced by the narcotic. However, the administration of nalorphine or levallorphan in these circumstances is not innocuous. If the depression is not due primarily to a morphine-like drug, it may be increased by a specific narcotic antagonist, since both nalorphine and levallorphan produce sedation and respiratory depression. Similarly if the depression was not due to a specific narcotic antagonist, the depression may be increased by nalorphine or levallorphan.

Table 2. Effect of Morphine Antagonists on the Oxygen Uptake of 6 Subjects Depressed by Morphine (Mean ± Standard Error of Mean)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Oxygen Consumption (ml./minute)</th>
<th>Per Cent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>Antagonist</td>
</tr>
<tr>
<td>5</td>
<td>276 ± 16</td>
<td>Saline (Placebo)</td>
</tr>
<tr>
<td>4</td>
<td>231 ± 11</td>
<td>Nalorphine, 7 mg.</td>
</tr>
<tr>
<td>4</td>
<td>273 ± 39</td>
<td>Methylphenidate, 10 mg.</td>
</tr>
<tr>
<td>6</td>
<td>262 ± 17</td>
<td>Methylphenidate, 30 mg.</td>
</tr>
</tbody>
</table>

* Significant difference at P < 0.05 by t-test for paired replicates.
pression is the result of a single therapeutic dose of narcotic, only partial or transient antagonism could be expected at most from a specific narcotic antagonist and the antagonism may be limited to respiratory stimulation. This study indicates that methylphenidate is equally as effective as nalorphine in antagonizing the respiratory depression of therapeutic doses of morphine and is more effective in antagonizing psychic depression. It would, therefore, seem wiser to treat “mixed” depressions as well as excessive depression from a therapeutic narcotic dose with a nonspecific antagonist, even though the increased oxygen uptake of methylphenidate might conceivably be disadvantageous in some circumstances. Our data support the recommendation of Eckenhoff and Oech that a specific narcotic antagonist “should be reserved for the treatment of severe respiratory depression from a narcotic.”

Methylphenidate was selected as the nonspecific antagonist in this study because of its demonstrated analeptic effect in thiopental depression and its relative freedom from convulsive activity. However, the results with methylphenidate probably apply equally well to other nonspecific analeptics. Becker, Nasr, and Schwab in a similar study on healthy subjects reported that nikethamide was a more effective antagonist of respiratory depression induced by therapeutic doses of morphine and levorphanol that was nalorphine or levallophan.

In this study, antagonism of depressed respiration was equal but incomplete with both antagonists. Antagonism of sedation was marked with methylphenidate, slight or absent with nalorphine. This comparison provides additional evidence of the failure of nalorphine to antagonize completely the effects of therapeutic doses of narcotics as well as suggesting the existence of differential antagonism of the various parameters of narcotic action by specific narcotic antagonists. The degree of respiratory stimulation by nalorphine in this study was greater than that reported previously using therapeutic narcotic doses. This may be related in some way to the intravenous route of administration since the only studies which demonstrated a lesser respiratory depression after a narcotic-narcotic antagonist mixture compared to the narcotic alone, employed the intravenous route. No difference could be demonstrated when drugs were given intramuscularly or subcutaneously.

Our data are essentially in agreement with those reported by Huggins et al. who administered 5, 10, 25 mg of nalorphine intravenously after 90 mg of morphine in healthy subjects. They found no significant increase in oxygen uptake and no respiratory stimulation after 5 mg of nalorphine, respiratory stimulation but no increase in oxygen uptake after 10 mg and an increase in both after 25 mg of nalorphine.

Summary

The comparative efficacy of a specific narcotic antagonist (nalorphine) and a nonspecific narcotic antagonist (methylphenidate) in antagonizing morphine-induced respiratory depression was determined in 6 healthy subjects. It was found that 30 mg of methylphenidate was as effective as 7 mg of nalorphine in antagonizing the respiratory depression of 10 mg of morphine. The antagonism by methylphenidate was associated with an increase in oxygen uptake and psychic stimulation. The antagonism by nalorphine was associated with no change in oxygen uptake and with persisting sedation. Reasons were given for advocating treatment of mild narcotic-induced depression with a nonspecific analeptic and treatment of severe narcotic depression with a specific narcotic antagonist.

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References

MYOCARDIAL INFARCTION Hypotension occurs in nearly 10 per cent of patients with myocardial infarction. An 80 per cent mortality results if the hypotension is not quickly reversed. The most important therapy is immediate oxygen administration and complete pain relief. Next in order of therapeutic value is levaterenol administered intravenously to maintain a blood pressure over 100 mm. of mercury in patients who were previously normotensive. Concentration of levaterenol should be increased in patients who have congestive heart failure in order to decrease the volume of fluid intake. (Heller, E. M.: Therapy of Hypotension in Acute Myocardial Infarction, Dis. Chest 40: 338 (Sept.) 1961.)

BLOOD PRESSURE BY PALPATION A method is given to determine brachial artery diastolic pressure by palpation during deflation of a sphygmomanometer cuff. External recordings of the brachial artery pulse. during decompression of an inflated sphygmomanometer cuff have consistently shown a characteristic change in the form of the pulse. This consists of a sharp spike on the upstroke, disappearing abruptly at the diastolic level. The nature and behavior of this spike at diastolic levels appear to be the graphic demonstration of a tactile phenomenon that enables the observer to estimate diastolic blood pressure by palpation. (Ensellberg, C. D.: Measurement of Diastolic Blood Pressure by Palpation, New Engl. J. Med. 265: 272 (Aug. 10) 1961.)