Reversal of Morphine Anesthesia with Naloxone

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Six hours after intravenous injection of morphine, 2 mg/kg, seven healthy adults received a ten-hour intravenous infusion of naloxone (3.66 µg/kg loading dose plus 3.66 µg/kg/hr), totaling 40 µg/kg. Immediately before administration of naloxone, resting minute ventilation (Ve) was 6.2 ± 0.4 (SE) l/min, end-tidal CO₂ tension (PETCO₂) 65 ± 3 torr, and the CO₂ response slope averaged only 0.5 ± 0.2 l/min/torr in one subject Ve decreased in response to CO₂. Plasma morphine concentration was 654 ± 93 ng/ml and correlated poorly with respiratory depression or mental alertness. One hour after starting the naloxone infusion, resting Ve was 6.8 ± 0.5 l/min, PETCO₂, 54 ± 1 torr, and CO₂ response slope 1.2 ± 0.1 l/min/torr. Mental vigilance testing, by repetitive verbal challenges, showed 100 ± 0 per cent correct responses during the control period, 50 ± 18 per cent immediately before naloxone, and 86 ± 6 per cent one hour later. Ve, PETCO₂, CO₂ response slope and displacement, and mental vigilance improved progressively 4 and 8 hours after starting the naloxone infusion. Twenty-one and one half hours after morphine injection, plasma concentration was 39 ± 13 ng/ml. At this time resting ventilatory values did not differ from control, but the CO₂ response curve remained significantly displaced. During naloxone infusion all subjects complained of bladder distention, and five vomited. Naloxone, 40 µg/kg/10 hours, as an antagonist to morphine, 2 mg/kg, adequately balances respiratory effects and emetic side-effects. (Key words: Analgesics, naloretic; morphine; Antagonists, naloretic; naloxone; Ventilation: morphine reversal.)

Naloxone is an opiate antagonist without intrinsic depressant properties and with minimal cardiovascular side-effects. Since the duration of action of naloxone is shorter than that of morphine, complete reversal without subsequent renarctization would require a very large naloxone dosage. Complete and rapid reversal of large opiate dosages is impractical, however, because of nausea, vomiting and, in postoperative patients, pain. With repeated smaller doses or continuous infusion one might obtain adequate respiration with minimal nausea and vomiting without renarctization.

Previous experience suggested that 40 µg/kg naloxone infused over ten hours would adequately reverse 2 mg/kg morphine in healthy volunteers. Using as criteria for adequate reversal a resting end-tidal CO₂ tension (PETCO₂) less than 55 torr, a CO₂ ventilatory response slope greater than 1 l/min/torr, and no deterioration of these values after stopping naloxone, our dosage is nearly optimal.

Methods

Our subjects were seven men participating in a study of the effects of morphine on cerebral vascular autoregulation. Informed consent to study naloxone reversal of their morphine anesthesia was obtained. The subjects were healthy, 21 to 27 years old; weights and heights ranged from 69.5 to 107.4 kg and 178 to 181 cm. All subjects were familiarized with the research laboratory and experimental equipment before the day of the study. Control respiratory measurements and vigilance tests were made on a day preceding the study.

The subjects fasted overnight. Control grip strength was measured with a hand dynamometer on the study day. In the morning each received 2 mg/kg morphine sulfate injected intravenously over 20 minutes. Ni-
turous oxide, oxygen, and d-tubocurarine main-
tained anesthesia. Ventilation was controlled
to maintain P\textsubscript{aCO\textsubscript{2}} at 40 torr. Blankets and
warming lights kept body temperature within
normal limits. The cerebral blood flow
studies lasted approximately 5 hours, after
which nitrous oxide was discontinued.

\textit{d-}Tubocurarine was reversed with neostig-
mime until each subject could lift his head
against gravity and hand-grip strength ex-
ceeded 50 per cent of control. After extuba-
tion of the trachea 15 to 30 minutes were
allowed for stabilization. Measurements of
resting ventilation, ventilatory response to
CO\textsubscript{2} and maximal voluntary ventilation
(MVV) followed. After removal of the mouth-
piece, vigilance was tested. Venous blood
was sampled for plasma morphine con-
centration (PMC). This sequence (hand-grip
strength, resting ventilation, CO\textsubscript{2} response,
MVV, mental vigilance and PMC) was re-
peated 6, 7\textfrac{1}{2}, 10\textfrac{1}{2}, 14\textfrac{1}{2}, and 21\textfrac{1}{2} hours after
morphine injection. These times correspond
to just before naloxone infusion; 1, 4, and 8
hours after starting the 10-hour naloxone
infusion; and 5 hours after finishing the
infusion.

Naloxone reversal began after the 6-hour
post-morphine measurements. Naloxone, 3.66 \mu g/kg, was injected intravenously over
15 minutes, followed by 3.66 \mu g/kg/hr for 10
hours. The ten-hour naloxone dose was di-
luted with saline solution to 50 ml and
continuously infused with a constant-rate
Harvard Intravenous Syringe Pump. Thus,
after one hour, 7.32 \mu g/kg (or 18 per cent of
the total naloxone dose) had been infused;
after four hours, 18.3 \mu g/kg (46 per cent);
after eight hours, 32.9 \mu g/kg (82 per cent).

\begin{table}[h]
\centering
\caption{Reversal of Morphine Anesthesia in Seven Subjects (Means ± SE)}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Period} & \textbf{Hours after Morphine} & \textbf{Plasma Morphine Concentration (ng/ml)} & \textbf{Resting P\textsubscript{aCO\textsubscript{2}}, (torr)} & \textbf{CO\textsubscript{2} Response Slope (1/min/torr)} & \textbf{Vigilance Score (Per Cent Correct)} \\
\hline
Control & - & - & 4.4 ± 1 & 2.5 ± 0.5 & 100 ± 0 \\
Pre-naloxone & 6 & 654 ± 93 & 65 ± 3* & 0.5 ± 0.2* & 50 ± 18 \\
During naloxone & & & & & \\
1 hour & 7\textfrac{1}{2} & 477 ± 95 & 54 ± 1* & 1.2 ± 0.1* & 86 ± 6 \\
4 hours & 10\textfrac{1}{2} & 336 ± 75 & 52 ± 1* & 1.6 ± 0.2 & 94 ± 4 \\
8 hours & 14\textfrac{1}{2} & 123 ± 40 & 47 ± 1* & 1.6 ± 0.2 & 99 ± 1 \\
Post-naloxone & 21\textfrac{1}{2} & 39 ± 13 & 44 ± 2 & 1.9 ± 0.3 & - \\
\hline
\end{tabular}
\end{table}

* Significantly different from control, \( P < 0.05 \).

Respiratory Measurements

Respiratory measurements were made by a
modification of the Eckenhoff technique as
previously described.\textsuperscript{2} CO\textsubscript{2} was absorbed in the
expiratory circuit. A Texas Instruments

\textbf{Figure 1.} Ventilatory response to
CO\textsubscript{2} after morphine, 2 mg/kg, and
antagonism by naloxone infusion, 40 \mu g/kg.
NALOXONE REVERSAL OF MORPHINE

Fig. 2. Individual responses to CO₂ after morphine, 2 mg/kg. Response curves are labeled with the subjects' initials. Curve C is the averaged control. A (above), pre-naloxone; B (below), antagonism by naloxone.

Servoriter continuously recorded ventilation and \( \text{PETCO}_2 \). MVV was determined over 15 seconds. CO₂ response slopes were determined by calculating the least-squares regression equation for the curve between 12.5 and 30 l/min.

VIGILANCE TEST

A variation of Mackworth's technique of measuring mental altertness was used.** Two hundred fifty digits containing 51 randomly placed "two's" were tape-recorded. When the recorder was played, these numbers were presented every two seconds in a regular monotonous fashion. Subjects were instructed to answer "yes" after "two" and "no" after all other numbers. Responses were scored as correct or not correct. Failure to respond was scored as incorrect; subjects were verbally awakened after three consecutive non-responses. Vigilance test results are reported as percentages of correct responses.

PLASMA MORPHINE CONCENTRATION

Two milliliters of blood were drawn into a heparinized syringe three times during the cerebral blood flow study and once during each respiratory study period, and placed in ice. Plasma morphine concentrations (PMC) were determined with the Abuscreen† radioimmunoassay by a technique similar to that of Catlin et al.† An exponential equation of PMC as a function of time was fit to each individual's data by least-squares method. Averaging time constants and intercepts of each subject's curve yielded average PMC decay. PMC were normalized according to initial concentration. Values interpolated at the mid-time of each CO₂ response were tested for correlation with respiratory data.

** Adapted by Nilly Adam, Ph.D., Department of Psychology, University of Pennsylvania.

† Available from Roche Diagnostics, Division of Hoffman-La Roche, Inc., Nutley, New Jersey 07110.
Two-dimensional analysis of variance with critical difference testing at \( P < .05 \) was used to compare data at different times. \( r \) values refer to coefficient of correlation.

**Results**

Results are grouped into four time periods: control, pre-naloxone, during naloxone, and post-naloxone. Pre-naloxone measurements were made 297 to 424 (average 353) minutes after morphine injection, depending on the time needed to complete cerebral blood flow measurements. Table 1 presents mean results for all time periods. Figure 1 shows mean CO\(_2\)-ventilatory response curves for each time period.

**CONTROL**

Measurements for all subjects were within accepted normal limits. Pulse rate was \( 70 \pm 3 \) (SE) min and blood pressure \( 120 \pm 4/73 \pm 3 \) torr. In addition to the respiratory data reported in table 1, resting ventilatory minute volume (\( V_E \)) was \( 9.8 \pm 0.9 \) l/min at a frequency (f) of \( 11.5 \pm 1.3 \) breaths/min. Anatomic deadspace (\( V_D \)) was \( 0.184 \pm 0.222 \) l. CO\(_2\) challenge brought PET\(_{CO_2}\) at \( 20 \) l/min to \( 52 \pm 1 \) torr. Maximal voluntary ventilation (MVV) was \( 176 \pm 15 \) l/min. Grip strength was \( 48 \pm 3 \) kg.

**PRE-NALOXONE**

Before respiratory measurements all subjects responded to voice commands and breathed spontaneously. Mean grip strength was \( 33 \pm 4 \) kg (65 per cent of control). Oral temperatures averaged \( 36.8 \pm 0.1 \) C, pulse rates \( 82 \pm 4 \) /min, and blood pressures \( 133 \pm 8/77 \pm 4 \) torr. Pulse rate was significantly greater than control, but blood pressure was not.

CO\(_2\) challenge disclosed a very heterogeneous group (fig. 2A). One subject (MB) had no change in CO\(_2\) response slope and a poor vigilance score, one (WH) with a perfect vigilance score had a poor ventilatory response to CO\(_2\), and one subject (RF) could neither cooperate for vigilance testing nor respond to CO\(_2\) challenge. RF’s study was terminated during CO\(_2\) response testing when his \( V_E \) fell to 1.8 l/min; his breathing increased immediately after naloxone injection. CO\(_2\) response slopes in the seven subjects ranged from \(-0.15 \) to \( 1.30 \) l/min/torr, while vigilance scores ranged from 0 to 100 per cent.

Resting \( V_E \) averaged \( 6.2 \pm 0.4 \) l/min and respiratory frequency, \( 9.1 \pm 0.8 \) breaths/min. \( V_E \) and PET\(_{CO_2}\) differed significantly from control. The subject (RF) with the greatest PMC had the most depressed ventilatory response to CO\(_2\); however, CO\(_2\) response slope correlated poorly with actual time from morphine injection (\( r = 0.59 \)) or PMC (\( r = 0.47 \)). Percentage of control grip strength (\( r = 0.49 \) and vigilance score (\( r = 0.00 \)) also did not correlate with CO\(_2\) response. Maximal voluntary ventilation was \( 75 \pm 25 \) l/min. Two subjects (FZ, TS) were too sleepy to cooperate adequately and breathed only 26 and 20 l/min, respectively. Anatomic deadspace was \( 0.234 \pm 0.029 \) l, not significantly different from control. No subject vomited or complained of bladder discomfort before infusion of naloxone.

**DURING NALOXONE: ONE HOUR**

The initial naloxone injection immediately increased the consciousness level in all subjects; two subjects complained of nausea and another vomited during this period. Blood pressure was unchanged at \( 131 \pm 8/75 \pm 3 \) torr; pulse rate was \( 83 \pm 5 \) /min, still significantly greater than control. Grip strength was \( 86 \pm 3 \) per cent of control. All subjects complained of bladder discomfort; none could void more than 100 ml at once despite a full bladder.

Individual response curves are shown in fig. 2B. Comparison with pre-naloxone values shows that the CO\(_2\) response slope is significantly steeper, the PET\(_{CO_2}\) shift at \( 20 \) l/min significantly less, and the vigilance score greatly improved. Resting \( V_E \) was \( 6.8 \pm 0.5 \) l/min, 0.6 l/min greater than pre-naloxone, but still significantly less than control. Respiratory frequency was \( 11.4 \pm 1.2 \) breaths/min and \( V_D \) 0.198 \( \pm 0.034 \) l. PMC was \( 477 \pm 95 \) ng/ml and again correlated poorly with vigilance score (\( r = 0.33 \)), resting \( V_E \) (\( r = 0.03 \)), or CO\(_2\) response slope (\( r = 0.54 \)).
DURING NALOXONE: FOUR HOURS

All subjects were more alert and comfortable than during the previous measurement period. Although five subjects vomited, only two vomited several times. All had voided sufficiently to relieve their bladder discomfort. Pulse and blood pressure were 79 ± 9/min and 129 ± 4/76 ± 2 torr, not significantly different from control. Grip strength was 92 ± 5 per cent of control. Vigilance testing yielded 94 ± 4 per cent correct responses. Resting $V_E$ was 8.0 ± 0.5 l/min and $f$, 13.2 ± 1.0. Anatomic deadspace was 0.186 ± 0.027 l. CO$_2$ response continued to improve. Response slope was not significantly different from control, but PET$_{CO_2}$ displacement at 20 l/min was. Maximal voluntary ventilation was 116 ± 16 l/min, with all subjects above 60 l/min.

DURING NALOXONE: EIGHT HOURS

All subjects were comfortable and had stopped vomiting. Six subjects had perfect vigilance scores and one was 95 per cent correct. Resting ventilatory measurements were $V_E$ 8.4 ± 0.6 l/min and $f$, 15.9 ± 1.8 breaths/min. Resting PET$_{CO_2}$ was significantly less than during naloxone, four hours, but still significantly greater than control. The averaged CO$_2$ response curve was significantly improved from during naloxone, four hours, but still significantly shifted from control. VD$_a$ was 0.145 ± 0.015 l.

POST-NALOXONE

All subjects were alert, hungry, and desired to get out of bed. Resting ventilatory measurements were $V_E$ 10.0 ± 1.0 l/min and $f$, 14.8 ± 1.9 breaths/min. PET$_{CO_2}$ was significantly less than during naloxone, eight hours. No resting ventilatory value differed significantly from control. The averaged CO$_2$ response curve was still shifted significantly to the right of control.

PLASMA MORPHINE CONCENTRATION

All measured plasma morphine concentrations, as well as the least-square best-fit exponential curve, are plotted in figure 3. The equation of this curve is PMC = 1980 e$^{-0.00236T}$, when $T$ is time in minutes and PMC is expressed in ng/ml. The correlation coefficient of all data with this curve is 0.986. Individual time constants ranged from 234 to 543 per minute. The average half-life of morphine in plasma is 207 minutes.

Discussion

Many anesthesiologists use morphine in large intravenous doses (1–3 mg/kg) for anesthesia in high-risk patients. The major side-
effect of this technique is profound postoperative respiratory depression, generally necessitating mechanical ventilation for 6 to 24 hours. Alternatively, a narcotic antagonist can reverse morphine's respiratory depression. Naloxone is an opiate antagonist without intrinsic depressant properties and with minimal cardiovascular effects. Rapid, complete reversal of morphine anesthesia, however, is not desirable, because analgesia is also reversed and recurrent waves of vomiting precipitated.

Lecky and Bush (Lecky, J.H., and Bush, G.L., personal communication) investigated the effects of 55 µg/kg naloxone infused over ten hours to antagonize 3 mg/kg morphine in non-operative volunteers, and found nearly adequate reversal. Longnecker et al.7 after studying non-cardiothoracic patients, recommend 15 µg/kg naloxone (5 µg iv plus 10 µg im) to reverse 1.4 mg/kg morphine. Volunteers studied by Wong et al.8 needed an average of 40 µg/kg intravenously in divided doses to reverse 2 mg/kg morphine. These data and our clinical observations led us to choose 40 µg/kg naloxone infused over ten hours as the reversal dose for a routine morphine anesthesia dose of 2 mg/kg.

The duration of action of naloxone is shorter than that of morphine. Jasinski9 detected antagonist activity for 9 hours after 15 mg naloxone administered subcutaneously. Longnecker7 found 5 µg/kg naloxone iv effective for 79 minutes and 10 µg/kg effective for 99 minutes in reversing the respiratory depression produced by morphine. Hasbrouck's data show 60 to 90 minutes of respiratory effect after 2.5 µg/kg of naloxone.10 Adequate antagonism of anesthetic doses of morphine with naloxone requires large-dose subcutaneous or intramuscular injection, repeated intravenous injections, or constant intravenous infusion. Naloxone absorption after subcutaneous or intramuscular injection is probably variable in postoperative patients, so we chose intravenous infusion.

Morphine is a long-acting drug. Using a sensitive radioimmunoassay, we have found PNC to decrease in first-order fashion, with a half-life of 207 minutes. Although different subjects metabolized morphine at different rates, 21½ hours after injection all had easily measurable plasma concentrations. That these were pharmacologically active is evidenced by the significantly shifted CO2 response curve. Spector11 has detected morphine in plasma three days after an injection of 10 mg/70 kg. Our PMC are consistent with those reported by Spector,11 but are larger than levels obtained by less sensitive fluorometric assays.12,13 Our assay is sensitive to 10 ng/ml. It does not detect naloxone in the concentrations we used,13 but does detect morphine glucuronide. Magnitudes of respiratory depression at similar plasma morphine concentrations varied.

Spontaneous ventilation after large doses of morphine without opioid antagonism is hazardous. Six hours after morphine injection, our healthy subjects had greatly compromised ventilation. Resting PETCO2's ranged from 57 to 75 torr, indicating decreased ventilation. Flattening of their CO2 response curves indicates a poor response to stress; one subject even decreased his ventilation when challenged with CO2. Moderate doses of morphine have previously been shown to displace the CO2–ventilatory response curve with little or no change in slope.13,14 Our results show that morphine, like other CNS depressants, decreases the responsiveness to CO2, i.e., flattens the CO2 response curve slope, as sleep-inducing doses are reached. Respiratory depression is difficult to assess except by direct measurement of ventilation and arterial or expired gas tensions. Particularly, it is dangerous to rely on level of consciousness and mental alertness. Our subjects had poor correlation between alertness and respiratory depression.

Longnecker observed 50 episodes of nausea and vomiting after 79 injections of naloxone (5 or 10 µg/kg).7 Naloxone does not cause nausea and vomiting in unmedicated subjects.9 Although emesis may occur after small doses of morphine, especially in ambulatory patients, vomiting is not a reported complication of morphine anesthesia. Emesis occurred in our subjects during morphine reversal while breathing spontaneously with elevated PETCO2's. Emesis was not due to rapid Pco2 changes because it occurred in Wong's subjects, whose PETCO2's were maintained 1–3 torr below the resting value.6
Longnecker proposed an acute abstinence syndrome to explain reversal emesis,7 however, our subjects showed no evidence of acute tolerance to morphine's respiratory effects. Two hours after 10 mg morphine, iv, Spector's subjects had approximately the same PMC as our subjects after 2½ hours,11 yet the respiratory depression in our subjects at 21½ hours was more than that which occurs two hours after 15 mg morphine, iv.15

If a naloxone dosage which adequately antagonizes respiratory depression but minimizes vomiting and pain is sought, criteria for adequate reversal must be set. We feel that adequate criteria include: a normal slope to the CO₂–ventilatory response curve, resting P_co₂ less than 55 torr, and no deterioration of these values after stopping naloxone. One hour after starting the infusion of naloxone our subjects' respiratory responses were within the normal range, but several resting P_eto2's exceeded 55 torr. The initial naloxone dosage could be increased to 5–7 μg/kg, but, as shown by Longnecker,7 this will greatly increase the incidence of emesis. Balancing our subjects' normal postnaloxone CO₂ response slopes (the most important criterion) against the incidence of vomiting, our dosages are near optimal. By four hours all subjects met the above criteria. No narcotic rebound was detected. Regardless of naloxone dosage, close observation is required for several hours when spontaneous ventilation follows morphine anesthesia.

References