

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 μ g/kg loading dose plus 3.66 μ g/kg/hr), totaling 40 μ g/kg. Immediately before administration of naloxone, resting minute ventilation (\dot{V}_E) was 6.2 ± 0.4 (SE) l/min, end-tidal CO₂ tension (P_{ETCO_2}) 65 ± 3 torr, and the CO₂ response slope averaged only 0.5 ± 0.2 l/min/torr; in one subject \dot{V}_E 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 \dot{V}_E was 6.8 ± 0.5 l/min, P_{ETCO_2} 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. \dot{V}_E , P_{ETCO_2} , 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 μ g/kg/10 hours, as an antagonist to morphine, 2 mg/kg, adequately balances respiratory effects and emetic side-effects. (Key words: Analgesics, narcotic; morphine; Antagonists, narcotic; naloxone; Ventilation: morphine reversal.)

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NALOXONE is an opiate antagonist without intrinsic depressant properties and with minimal cardiovascular side-effects.¹ Since the duration of action of naloxone is shorter than that of morphine, complete reversal without subsequent reanarcotization would require very large naloxone dosage. Complete and rapid reversal of large opiate dosages is impractical, however, because of nausea and vomiting and, in postoperative patients, pain. With repeated smaller doses or continuous infusion one might obtain adequate respiration with minimal nausea and vomiting without reanarcotization.

Previous experience suggested that 40 μ g/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 (P_{ETCO_2}) 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.² 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-

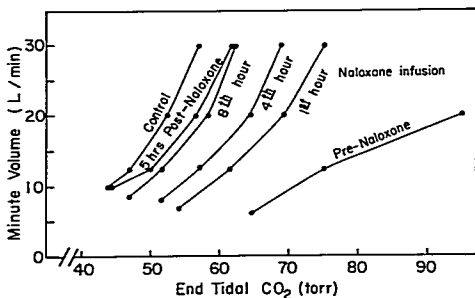


FIG. 1. Ventilatory response to CO_2 after morphine, 2 mg/kg, and antagonism by naloxone infusion, 40 $\mu\text{g}/\text{kg}$.

trous oxide, oxygen, and *d*-tubocurarine maintained anesthesia. Ventilation was controlled to maintain Pa_{CO_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. *d*-Tubocurarine was reversed with neostigmine until each subject could lift his head against gravity and hand-grip strength exceeded 50 per cent of control. After extubation of the trachea 15 to 30 minutes were allowed for stabilization. Measurements of resting ventilation, ventilatory response to CO_2 , and maximal voluntary ventilation (MVV) followed. After removal of the mouthpiece, vigilance was tested. Venous blood was sampled for plasma morphine concentration (PMC). This sequence (hand-grip strength, resting ventilation, CO_2 response, MVV, mental vigilance and PMC) was repeated 6, 7½, 10½, 14½, and 21½ 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 $\mu\text{g}/\text{kg}$, was injected intravenously over 15 minutes, followed by 3.66 $\mu\text{g}/\text{kg}/\text{hr}$ for 10 hours. The ten-hour naloxone dose was diluted with saline solution to 50 ml and continuously infused with a constant-rate Harvard Intravenous Syringe Pump. Thus after one hour, 7.32 $\mu\text{g}/\text{kg}$ (or 18 per cent of the total naloxone dose) had been infused; after four hours, 18.3 $\mu\text{g}/\text{kg}$ (46 per cent); after eight hours, 32.9 $\mu\text{g}/\text{kg}$ (82 per cent).

RESPIRATORY MEASUREMENTS

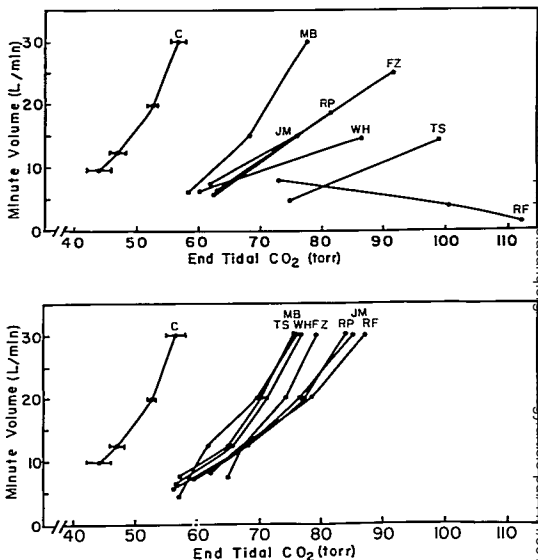
Respiratory measurements were made by modification of the Eckenhoff technique as previously described.³ CO_2 was absorbed in the expiratory circuit. A Texas Instrument

TABLE I. Reversal of Morphine Anesthesia in Seven Subjects (Means \pm SE)

Period	Hours after Morphine	Plasma Morphine Concentration (ng/ml)	Resting P_{ETCO_2} (torr)	CO_2 Response Slope (l/min/torr)	Vigilance Score (Per Cent Correct)
Control	—	—	44 \pm 1	2.5 \pm 0.5	100 \pm 0
Pre-naloxone	6	654 \pm 93	65 \pm 3*	0.5 \pm 0.2*	50 \pm 18
During naloxone					
1 hour	7½	477 \pm 95	54 \pm 1*	1.2 \pm 0.1*	86 \pm 6
4 hours	10½	336 \pm 75	52 \pm 1*	1.6 \pm 0.2	94 \pm 4
8 hours	14½	123 \pm 40	47 \pm 1*	1.6 \pm 0.2	99 \pm 1
Post-naloxone	21½	39 \pm 13	44 \pm 2	1.9 \pm 0.3	—

* Significantly different from control, $P < 0.05$.

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), prenaloxone; B (below), antagonism by naloxone.



Servoriter continuously recorded ventilation and PET_{CO_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 technique⁴ of measuring mental alertness 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 consecu-

tive 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.*⁵ 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 ± 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 (\dot{V}_E) was 9.8 ± 0.9 l/min at a frequency (f) of 11.5 ± 1.3 breaths/min. Anatomic deadspace (VD_A) was 0.184 ± 0.022 l. CO_2 challenge brought PET_{CO_2} at 20 l/min to 52 ± 1 torr. Maximal voluntary ventilation (MVV) was 176 ± 15 l/min. Grip strength was 48 ± 3 kg.

PRE-NALOXONE

Before respiratory measurements all subjects responded to voice commands and breathed spontaneously. Mean grip strength was 33 ± 4 kg (68 per cent of control). Oral temperatures averaged 36.8 ± 0.1 C, pulse rates 82 ± 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 \dot{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 1.20 l/min/torr while vigilance scores ranged from 0 to 100 per cent.

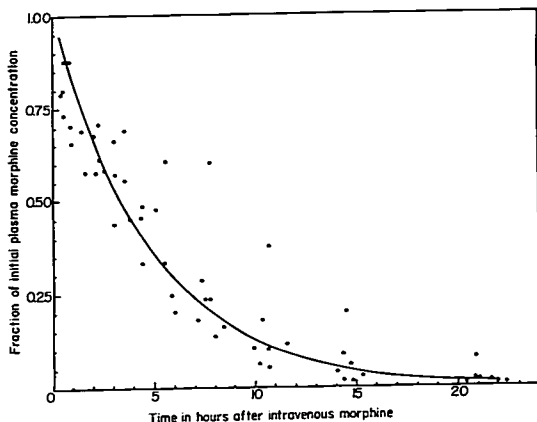
Resting \dot{V}_E averaged 6.2 ± 0.4 l/min and respiratory frequency, 9.1 ± 0.8 breaths/min. \dot{V}_E and PET_{CO_2} differed significantly from control. The subject (RF) with the greatest PMC had the most depressed ventilatory response to CO_2 ; however, CO_2 response slope correlated poorly with actual time from morphine injection ($r = 0.59$) or PMC ($r = 0.47$). Percentage of control grip strength ($r = 0.49$) and vigilance score ($r = 0.000$) also did not correlate with CO_2 response. Maximal voluntary ventilation was 75 ± 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 ± 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 $131 \pm 8/75 \pm 5$ torr; pulse rate was 83 ± 5 /min, still significantly greater than control. Grip strength was 86 ± 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 \dot{V}_E was 6.8 ± 0.6 l/min, 0.6 l/min greater than pre-naloxone, but still significantly less than control. Respiratory frequency was 11.4 ± 1.2 breaths/min and VD_A 0.198 ± 0.034 l. PMC was 477 ± 95 ng/ml and again correlated poorly with vigilance score ($r = 0.32$), resting \dot{V}_E ($r = 0.03$), or CO_2 response slope ($r = 0.54$).

FIG. 3. Decline in plasma morphine concentration after intravenous injection.



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 $129 \pm 4/76 \pm 2$ 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 \dot{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 \dot{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 \dot{V}_E 10.0 ± 1.0 l/min and 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 $\text{PMC} = 1980 e^{-0.002367T}$, 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.⁶ The major side-

effect of this technique is profound post-operative 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 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ intravenously in divided doses to reverse 2 mg/kg morphine. These data and our clinical observations led us to choose 40 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ naloxone iv effective for 79 minutes and 10 $\mu\text{g}/\text{kg}$ effective for 99 minutes in reversing the respiratory depression produced by morphine. Hasbrouk's data show 60 to 90 minutes of respiratory effect after 2.5 $\mu\text{g}/\text{kg}$ 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 radiomunoassay, we have found PMC 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.^{8,12} Our assay is sensitive to 10 ng/ml. It does not detect naloxone at 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.^{3,14} 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 $\mu\text{g}/\text{kg}$).⁷ Naloxone does not cause nausea and vomiting in unpremedicated 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 due to rapid P_{CO₂} changes because it occurred in Wong's subjects, whose PETCO₂'s were maintained 1-3 torr below the resting value.

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 2½ 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_{CO}, 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 PETCO₂'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 post-naloxone 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.

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