Effect of Morphine and n-Allylnormorphine on Cerebral Hemodynamics and Oxygen Metabolism

By John H. Moyer, M.D., Robert Pontius, M.D., George Morris, M.D., and Robert Hershberger, M.D.

The cerebral metabolic response to intravenously administered morphine was studied in human volunteers. Cerebral blood flow and cerebral vascular resistance were not altered by this drug although cerebral oxygen uptake was markedly depressed as a result of a decreased extraction of oxygen from the blood circulating through the brain. This response was rapidly reversed following the administration of n-allylnormorphine.

What are the effects of morphine on cerebral hemodynamics and cerebral metabolism in man, and how are these effects altered by the administration of n-allylnormorphine (Nalline), a morphine antagonist? Does n-allylnormorphine selectively antagonize the respiratory depressant effect of morphine overdosage, or does it antagonize the general cerebral metabolic response to morphine? Before these questions can be answered it is necessary to know the effect of large doses of morphine on cerebral blood flow and cerebral oxygen metabolism.

Although morphine is one of the oldest drugs in common use today, very little is known about the cerebral hemodynamic and metabolic responses to this agent in man. Such observations would not only assist in a better understanding of the pharmacodynamics of morphine, but in addition would give information relative to the mode of action of n-allylnormorphine. The present study is concerned with observations of the effect of intravenous morphine on cerebral hemodynamics and cerebral oxygen metabolism and of the ability of n-allylnormorphine to alter these responses.

Methods

Seven male volunteers 17 to 42 years of age were studied. With the subject resting comfortably in the supine position, indwelling needles were placed in the superior jugular bulb and the femoral artery. The nitrous oxide technic of Kety and Schmidt was used in determining cerebral blood flow. Measurements were made of pulse rate, respiratory rate, and mean arterial blood pressure, the last by direct arterial manometry. The methods and analytic procedures have been described previously. The partial pressure of carbon dioxide was determined with the aid of a Van Slyke nomogram. The cerebral oxygen consumption (CMRO$_2$) was determined by multiplying cerebral blood flow by the arterial venous oxygen difference. Cerebral vascular resistance (CVR), as presented in the current studies, is a simple ratio of mean arterial blood pressure divided by cerebral blood flow in ml. per 100 Gm. of brain per minute, each patient serving as his own control.

After suitable control observations were made, 6O mg. of morphine sulfate were administered intravenously over a 10-minute period. After an interval of 10 to 35 minutes, observations on cerebral hemodynamics and cerebral oxygen uptake were repeated. Then, 25 mg. of n-allylnormorphine were given slowly by the intravenous route. Cerebral blood flow determinations again were made after 15 to 20 minutes.

During these experiments a respirator was available at all times, since marked respiratory depression was anticipated, although it was not observed. However, during the administration of morphine the subject developed severe laryngospasm, which was not anticipated. Disaster was averted only by direct laryngoscopy carried out within a few seconds after the onset of the laryngospasm. By the time the air way was re-established, the pulse had become rapid and thready, the subject was severely cyanotic and partially comatose, and the mean arterial blood pressure had decreased to 30 mm. Hg. These alterations were quickly reversed as pulmonary function returned. There were no residual effects. Observations on cerebral blood flow were not repeated after...
TABLE 1.—Effect of Morphine on Cerebral Hemodynamics and Cerebral Oxygen Metabolism

<table>
<thead>
<tr>
<th>Patient, sex, age</th>
<th>Mean blood pressure mm. Hg</th>
<th>Pulse rate</th>
<th>Cerebral blood flow ml./100 Gm./min.</th>
<th>Cerebrovascular resistance</th>
<th>Cerebral oxygen uptake*</th>
<th>Hematocrit</th>
<th>Blood O₂ Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>DM</td>
<td>DN</td>
<td>C</td>
<td>DM</td>
<td>DN</td>
<td>C</td>
</tr>
<tr>
<td>1. H.D. M, 17</td>
<td>81</td>
<td>80</td>
<td>83</td>
<td>102</td>
<td>88</td>
<td>99</td>
<td>53.7</td>
</tr>
<tr>
<td>2. H.E. M, 24</td>
<td>102</td>
<td>91</td>
<td>96</td>
<td>81</td>
<td>92</td>
<td>88</td>
<td>64.4</td>
</tr>
<tr>
<td>3. Me.C. M, 30</td>
<td>91</td>
<td>91</td>
<td>95</td>
<td>88</td>
<td>86</td>
<td>88</td>
<td>42.0</td>
</tr>
<tr>
<td>4. G.L. M, 42</td>
<td>89</td>
<td>89</td>
<td>104</td>
<td>110</td>
<td>110</td>
<td>117</td>
<td>30.9</td>
</tr>
<tr>
<td>5. N.N. F, 35</td>
<td>110</td>
<td>92</td>
<td>92</td>
<td>96</td>
<td>96</td>
<td>96</td>
<td>48.2</td>
</tr>
<tr>
<td>6. J.J. M, 28</td>
<td>78</td>
<td>79</td>
<td>72</td>
<td>98</td>
<td>80</td>
<td>80</td>
<td>51.5</td>
</tr>
<tr>
<td>7. H. J. F, 32</td>
<td>82</td>
<td>62</td>
<td>—</td>
<td>—</td>
<td>69</td>
<td>57.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Mean 90 | 83 | 90 | 96 | 92 | 95 | 55.1 | 58.8 | 49.1 | 1.9 | 1.5 | 1.9 | 3.2 | 1.9 | 2.5 | 41 | 41 | 42 | 98 | 96 | 93 | 60 | 67 | 63

% of control 92 | 100 | 96 | 99 | 114 | 95 | 79 | 100 | 59 | 78 | 100 | 102 | 92 | 97 | 112 | 105

p Value† .10 | .50 | .50 | .50 | .30 | .50 | .20 | .20 | .20 | .40 | .20 | .50 | .30

p Value§ .04 | .40 | .40 | .50 | .20 | .20 | .10 | .20 | .20 | .30

C = Control observations.
DM = Observations made after the administration of 60 mg. of morphine intravenously.
DN = Observations made after the administration of 25 mg. of n-allylnormorphine.
* = ml./100 Gm. brain/minute.
† = Statistical analysis by R. A. Seibert.
‡ = p Value comparing post drug observations (morphine and n-allylnormorphine) with control observations.
§ = Comparing observations after n-allylnormorphine with those made after the administration of morphine using the latter observations as the reference point (control).

TABLE 2.—Effect of Morphine on Cerebral Blood Oxygen and Carbon Dioxide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arterial O₂ volume %</th>
<th>Venous O₂ volume %</th>
<th>Arterio-Venous O₂ volume %</th>
<th>Arterial CO₂ volume %</th>
<th>Venous CO₂ volume %</th>
<th>Arterial PCO₂ mm. Hg</th>
<th>Venous PCO₂ volume %</th>
<th>Time DM After morphine (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>DM</td>
<td>DN</td>
<td>C</td>
<td>DM</td>
<td>DN</td>
<td>C</td>
<td>DM</td>
</tr>
<tr>
<td>1. H.D.</td>
<td>16.9</td>
<td>15.9</td>
<td>14.9</td>
<td>9.9</td>
<td>12.5</td>
<td>10.1</td>
<td>7.0</td>
<td>3.4</td>
</tr>
<tr>
<td>2. H.E.</td>
<td>18.7</td>
<td>18.5</td>
<td>19.4</td>
<td>11.9</td>
<td>14.2</td>
<td>13.2</td>
<td>6.8</td>
<td>4.3</td>
</tr>
<tr>
<td>3. Me.C.</td>
<td>14.1</td>
<td>11.7</td>
<td>12.4</td>
<td>9.1</td>
<td>9.3</td>
<td>8.6</td>
<td>5.0</td>
<td>2.4</td>
</tr>
<tr>
<td>4. G.L.</td>
<td>15.1</td>
<td>14.1</td>
<td>14.8</td>
<td>7.6</td>
<td>10.5</td>
<td>9.3</td>
<td>7.5</td>
<td>3.6</td>
</tr>
<tr>
<td>5. N.N.</td>
<td>16.0</td>
<td>13.1</td>
<td>16.5</td>
<td>10.8</td>
<td>9.6</td>
<td>11.3</td>
<td>5.2</td>
<td>3.5</td>
</tr>
<tr>
<td>6. J.J.</td>
<td>16.5</td>
<td>15.0</td>
<td>16.5</td>
<td>11.0</td>
<td>12.9</td>
<td>11.0</td>
<td>5.5</td>
<td>2.1</td>
</tr>
<tr>
<td>7. H.J.</td>
<td>17.0</td>
<td>14.8</td>
<td>—</td>
<td>10.6</td>
<td>11.7</td>
<td>—</td>
<td>6.4</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Mean 16.3 | 14.7 | 15.8 | 10.1 | 11.5 | 10.6 | 6.2 | 3.2 | 5.2 | 46.7 | 50.9 | 49.2 | 52.6 | 53.5 | 54.3 | 43 | 52 | 45 | 50 | 57 | 56 | 56 | 27

% of control 90 | 97 | 90 | 114 | 105 | 52 | 84 | 100 | 105 | 102 | 103 | 121 | 105 | 114 | 112 |

p Value† .01 | .40 | .05 | .20 | .001 | .05 | .10 | .10 | .01 | .05 | .30 | .30 | .01 | .50 | .05 | .05 |

p Value§ .20 | .20 | .20 | .20 | .20 | .20 | .20 | .20 | .20 | .20 | .20 |

See table 1 for key to abbreviations.

the administration of morphine to this subject and consequently, he is not included in tables 1 and 2.

RESULTS

In 4 of the subjects, 60 mg. of morphine had very little effect on the arterial blood pressure, but reduced it more than 10 mm. Hg in the remaining 3. The average blood pressure response for the group was not statistically significant* (p < 0.10). The blood pressure

* p value of < 0.05 considered significant.
response to the administration of n-allylnormor-mophine was likewise erratic. Morphine given intravenously did not reduce the pulse rate, as might be expected with a dose of morphine of this magnitude, but marked sinus arrhythmia was frequently observed.

Following the administration of morphine, all but 1 of the subjects perspired rather profusely. The pupils constricted and respiration became shallow and irregular. Respiratory arrest was not observed and, except for the subject who developed laryngospasm, none of the subjects showed any signs of anoxia. After the administration of n-allylnormor-mophine (Nalline), the pupils dilated again. Very frequently the subjects perspired even more than after the administration of morphine. Respiration became regular, and the rate and depth increased sharply, so that the subjects appeared to hyperventilate for 2 to 3 minutes, as if the drug were acting as a respiratory stimulant much like \( \alpha \)-Lobeline.

Only 3 of the 7 subjects (H.D., M.c.C., and J.J.) showed marked somnolence after the administration of the morphine. Nevertheless it was quite characteristic that the subjects showed little concern over the indwelling needles or over any venous punctures that were done. However, after the n-allylnormorphine was given, the subjects became quite alert and were acutely aware of pain due to indwelling needles and venous punctures as well as any other trauma associated with the procedure. In addition, they frequently became very apprehensive by contrast with their docile attitude after the administration of morphine and before the administration of n-allylnormorphine.

For the group, neither morphine \( (p < 0.30) \) nor n-allylnormorphine \( (p < 0.50) \) affected cerebral blood flow to a statistically significant degree. However, when the individual observations are examined, there was an increase in cerebral blood flow in some subjects following morphine administration. This was usually associated with an increase in arterial partial pressure of carbon dioxide \( (p CO_2) \). Yet, 2 of the subjects (H.D., N.N.) showed an equally sharp increase in arterial \( p CO_2 \) without an increase in cerebral blood flow. For the group there was a slight reduction in cerebral vascular resistance (following morphine), but this was not statistically significant \( (p < 0.20) \).

Although the cerebral blood flow was not reduced, there was a marked and consistent depression in cerebral oxygen uptake (table 1), which was statistically significant \( (p < 0.01) \). This was due primarily to a reduction in the extraction of oxygen from the blood flowing through the brain, since the arterial-venous oxygen difference decreased \( (p < 0.001) \) at the same time that the oxygen content (table 2) of the blood coming from the brain increased \( (p < 0.05) \). These alterations occurred in the presence of a reduction in arterial oxygen content \( (p < 0.01) \). When the n-allylnormorphine was given, the cerebral oxygen uptake \( (CMRO_2) \) increased \( (p < 0.05) \) and returned to or towards the control values observed prior to the administration of morphine.

Although the rate of respiration was not seriously depressed following the administration of morphine, the depth of respiration decreased and the respiratory rhythm was irregular. This change was reflected in a significant reduction in arterial oxygen content \( (p < 0.01) \), arterial blood oxygen saturation \( (p < 0.01) \), and an increase in arterial blood \( pCO_2 \) \( (p < 0.01) \) and \( CO_2 \) content \( (p < 0.01) \). These responses were reversed after the n-allylnormorphine was given, so that when compared with the control values they were no longer altered significantly.

**Discussion**

The dose of morphine employed in these studies was rather large \((60 \text{ mg.})\) by the usual criteria, in order to effect definite alterations in respiration and cerebral function, so that the response to n-allylnormorphine could subsequently be evaluated more effectively. It was surprising that a greater effect on respiration was not produced by the large dose of morphine. Respiration was often shallow with a somewhat irregular respiratory rhythm, which appeared to be more under conscious regulation than usual if the subjects were not disturbed. Sometimes they would apparently forget to breathe, but when reminded of the fact, they would again pick up a more regular rhythm. When the n-allylnormorphine was given, the respiratory rate and depth increased...
Fig. 1. The effect of morphine and n-allylnormorphine on the cerebral circulation and cerebral oxygen metabolism.

sharply, indicating that the effect of morphine on the respiratory center had been reversed. In fact, the n-allylnormorphine appeared to have a temporary stimulating effect, so that respiratory movements were more marked than during the control period. This may have been a direct or an indirect effect on the sensitivity of the cerebral respiratory centers, which were responding to the increased $pCO_2$ and hypoxia that followed the morphine administration and were present when the n-allylnormorphine was given.

Observations of arterial-venous oxygen differences between the measurements of cerebral blood flow indicated a definite delay before the metabolic depressant effect of morphine occurred. The arterial-venous oxygen difference did not decrease during the first 10 to 15 minutes after the administration of morphine, but beyond 15 minutes it progressively decreased, usually reaching a minimum after 20 to 30 minutes. The only subject who failed to show a reduction in cerebral oxygen consumption was G.L., who was also the only subject on whom a cerebral blood flow determination was done in less than 20 minutes after the administration of morphine. A typical response to morphine and n-allylnormorphine is presented in figure 1.

The venous blood leaving the brain reflects the actual environment of the nerve tissues of the brain. Here the oxygen content increased significantly from 10.1 to 11.5 ml./100 ml. after the administration of morphine, but again fell to 10.6 after the administration of n-allylnormorphine. This sequence further reflects the cerebral metabolic depressant effect of morphine$^6,7$ on the human intact brain and the reversal of these effects with n-allylnormorphine.

The observations herewith reported appear to be quite consistent, although similar responses either to morphine or to n-allylnormorphine might not have been observed if smaller doses of morphine had been employed or if the drug had been given subcutaneously. It may well be that the drug does not have the same soporific effect when given by the intravenous route as compared to the subcutaneous route of administration or that 30 minutes is not an adequate period of time for the maximum soporific effect to develop. It is noteworthy that the only 3 subjects who showed marked somnolence (H.D., Mc.C., and J.J.) were the ones in whom cerebral oxygen uptake (CMRO$_2$) was reduced to the lowest absolute value. The cerebral hemodynamic and oxygen metabolic responses to morphine are qualitatively similar to the response to thiopental$^8$, which also depresses cerebral oxygen consumption even though the quantity of oxygen available to the neurons by way of the arterial blood
flow is not impaired. There are apparent quantitative differences in the clinical response, however, in that a reduction of cerebral oxygen uptake (of the degree noted in the current study on morphine) due to thiopental was associated with general anesthesia. By contrast to the cerebral hemodynamic and metabolic response to morphine and thiopental, chlorpromazine does not alter cerebral oxygen consumption (fig. 2). Any alterations in cerebral blood flow following the administration of chlorpromazine merely reflect changes in blood pressure rather than a direct effect of the drug. Clinical observations by us and others indicate that when smaller doses of morphine are used, the administration of n-allylnormorphine may be followed by an additive response rather than an antagonistic one.

**SUMMARY**

The effect of 60 mg of intravenously administered morphine has been studied in human volunteers. Although variations occur in individual patients, cerebral blood flow for the group is not altered significantly following the administration of morphine, but cerebral oxygen uptake (CMRO₂) is depressed to a significant degree in all. The reduction in CMRO₂ is associated with a reduction in arterial oxygen content, as well as a reduction in the extraction of oxygen from the blood circulating through the brain. These effects are rapidly (but only partly) reversed following the administration of n-allylnormorphine. Arterial blood oxygen saturation and oxygen content are decreased, while content and partial pressure of carbon dioxide are increased following the administration of morphine. The alterations in the blood flowing to the brain would tend to increase cerebral blood flow. This response was observed in a few instances, but was inconsistent. The alterations in blood oxygen and carbon dioxide concentrations resulting from the central respiratory depressant effects of morphine are reversed with n-allylnormorphine.

**SUMMARIO IN INTERLINGUA**

Le effecto de administrationes intravenose de 60 mg de morphina esseva studiate in voluntarios human. Ben que il occurre variationes in le casos individual, le fluxo de sanguine cerebral pro le gruppo integre non es alterate significative post le administration de morphina, sed le acception cerebral de oxygeno es deprimate a grados significative in omne casos. Le reduction del acception cerebral de oxygeno es associate con un reduction del contento arterial de oxygeno e etiam con un reduceci efficacia del extraction de oxygeno ab le sanguine que circula in le cerebro. Iste effectos es revertite rapide-, ben que solo partialmente, post le administration de n-allylnormorphina.

Le saturation oxygenic e le contento de oxygeno in le sanguine arterial es reducte, durante que le contento e le pression partial de bioxydo de carbon es augmentate post le administration de morphina. Le alterationes in le sanguine currente verso le cerebro tende apparentemente a augmentar le fluxo cerebral de sanguine. Iste responsa esseva observe in plure casos, sed le constatationes non esseva constante. Le alterationes del concentration sanguinee de oxygeno e bioxydo de carbon que resulta ab le effectos depressori de morphina super le systema respiratori central es revertite per n-allylnormorphina.

**REFERENCES**


Detection of multiple pulmonary embolism in patients with congestive heart failure is frequently difficult. Symptoms of such a complication include bouts of palpitation and arrhythmias, syncopal attacks, recurrent and particularly nocturnal episodes of dyspnea, acute anxiety, unexplained epigastric distress, and anginal syndromes. This study calls attention to the possibility of another clue to the diagnosis of this condition, namely the triad of tachycardia, digitalis intoxication, and resistance to mercurial diuresis. Satisfactory diuresis with mercurials appears to indicate that multiple pulmonary embolization is not present.

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