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.3 The partial pressure of carbon dioxide was determined with the aid of a Van Slyke nomogram. The cerebral oxygen consumption (CMRO₂) 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, 60 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 I 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 48.0</td>
</tr>
<tr>
<td>2. H.E. M, 24</td>
<td>102</td>
<td>91</td>
<td>96</td>
<td>91</td>
<td>82</td>
<td>88</td>
<td>64.4 58.4</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>86</td>
<td>42.0 50.2</td>
</tr>
<tr>
<td>4. G.L. M, 42</td>
<td>102</td>
<td>89</td>
<td>104</td>
<td>110</td>
<td>110</td>
<td>117</td>
<td>30.9 71.6</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 50.0</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 57.5</td>
</tr>
<tr>
<td>7. H. J. F, 32</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>79.6 57.6</td>
</tr>
</tbody>
</table>

Mean

| % of control | 90 | 92 | 90 | 96 | 92 | 95 | 51.5 58.8 | 49.1 | 1.9 | 1.5 | 1.93 | 2.1 | 1.9 | 2.1 | 56 | 41 | 42 | 41 | 42 | 96 | 88 | 93 | 60 | 67 | 63 |

% Value†

| 0.1 | 0.50 | .50 | 0.50 | .50 | .50 | 0.50 | .50 | .50 | .50 | .50 |

p Value‡

| .40 | .40 | .50 | .05 | .50 | .05 | .20 |

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>Arterial-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>101</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>18.6</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>9.5</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>16.7</td>
<td>10.6</td>
<td>11.7</td>
<td>10.6</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 | 6.5 | 3.2 | 6.5 | 46.7 | 50.9 | 49.2 | 52.6 | 53.5 | 54.3 | 43 | 52 | 45 | 50 | 57 | 56 | 27 |

% of control

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

p Value†

| .01 | .40 | .05 | .20 | .001 | .05 | .01 | .05 | .05 | .05 | .05 | .05 | .05 | .05 | .20 |

p Value‡

| .20 | .20 | .20 | .20 | .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- 
morphine 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 adminis-
tration of n-allylnormorphine (Nalline), the 
pupils dilated again. Very frequently the sub-
jects 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 hyper-
ventilate for 2 to 3 minutes, as if the drug were 
acting as a respiratory stimulant much like 
α-Lobeline.

Only 3 of the 7 subjects (H.D., Mc.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-allylnormor-
phine 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-allylnor-
morphine.

For the group, neither morphine (p < 0.30) 
or n-allylnormorphine (p < 0.50) affected 
cerebral blood flow to a statistically significant 
degree. However, when the individual observa-
tions 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 CO₂). Yet, 2 of 
the subjects (H.D., N.N.) showed an equally 
sharp increase in arterial p CO₂ without an 
increase in cerebral blood flow. For the group 
there was a slight reduction in cerebral vas-
cular 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 
pression in cerebral oxygen uptake (table 1), 
which was statistically significant (p < 0.01). 
This was due primarily to a reduction in the 
traction of oxygen from the blood flowing 
through the brain, since the arterial-venous 
xchange 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 con-
tent (p < 0.01). When the n-allylnormorphine 
was given, the cerebral oxygen uptake (CM-
RO₂) 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 administra-
tion of morphine, the depth of respiration 
decreased and the respiratory rhythm was ir-
regular. This change was reflected in a signi-
ificant reduction in arterial oxygen content 
(p < 0.01), arterial blood oxygen saturation 
(p < 0.01), and an increase in arterial blood 
pCO₂ (p < 0.01) and CO₂ 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 mg.) by the usual 
criteria, in order to effect definite alterations in 
respiration and cerebral function, so that the 
response to n-allylnormorphine could subse-
quently be evaluated more effectively. It was 
 surprising that a greater effect on respiration 
was not produced by the large dose of mor-
phine. Respiration was often shallow with a 
 somewhat irregular respiratory rhythm, which 
appeared to be more under conscious regula-
tion than usual if the subjects were not dis-
turbed. Sometimes they would apparently for-
get 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.

Fig. 2. Effect of chlorpromazine on cerebral hemodynamics and cerebral oxygen uptake (Moyer, J. H., Morris, G., Pontius, R., and Hershberger, R.: Circulation 14: 380, 1956).

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, 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 intravenos 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 altere significative post le administration de morfina, sed le acception cerebral de oxygeno es deprimite a grados significativo in omne casos. Le reduction del acception cerebral de oxygeno es associate con un reduction del contento arterial de oxygeno e etiam con un reduceit 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-allylnormorfhina.

Le saturation oxygene e le contento de oxygeno in le sanguine arterial es reduceit, durante que le contento e le pression partial de bioxydo de carbon es augmentate post le administration de morfina. Le alterationes in le sanguine currente verso le cerebro tende apparentemente a augmentar le fluxo cerebral de sanguine. Iste responsa esseva observate 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 morfina super le systema respiratoric central es revertite per n-allylnormorphina.

**REFERENCES**

Effect of Morphine and N-Allylnormorphine


Tench, W. R.: The Triad of Tachycardia, Digitalis Toxicity and Mercurial-Fast Edema in Congestive Heart Failure Complicated by Pulmonary Embolism. Am. J. Med. 19: 869 (Dec.), 1955. 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.

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

JOHN H. MOYER, ROBERT PONTIUS, GEORGE MORRIS and ROBERT HERSBERGER

Circulation. 1957;15:379-384
doi: 10.1161/01.CIR.15.3.379

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/15/3/379

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/