Effect of Chlorpromazine on Cerebral Hemodynamics and Cerebral Oxygen Metabolism in Man

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

With the Technical Assistance of C. Polk Smith

Cerebral blood flow frequently decreases following the intravenous administration of chlorpromazine, apparently a result of the reduction in arterial blood pressure. If arterial blood pressure does not decrease, cerebral blood flow is not altered. Chlorpromazine does not exert a depressant effect on cerebral oxygen consumption as morphine does.

Chlorpromazine exerts an inhibitory effect on numerous functions of the central nervous system, particularly on psychomotor and emotional activity. Differing from barbiturates, which have a predominant effect on the cerebrum, chlorpromazine seems to affect primarily the hypothalamic and medullary areas of the brain. It acts without producing the same degree of somnolence that barbiturates and opiates do. Since opiates and barbiturates depress cerebral oxygen uptake without affecting cerebral blood flow, it was decided to do similar studies before and after the administration of chlorpromazine in order to compare the response in normal control subjects.

Methods and Materials

Thirteen normotensive control subjects were studied. Nine of these received the chlorpromazine intravenously and 4 received it intramuscularly. The latter 4 subjects were selected because of the rather marked hypotensive responses observed after intravenous administration of the drug which in itself may reduce cerebral blood flow. Following intramuscular administration of chlorpromazine, the hypotensive effect was less marked than after intravenous administration. Therefore it was reasoned that the effects of blood pressure alterations due to chlorpromazine could be at least partially circumvented by giving the drug intramuscularly.

The subjects were studied in a fasting state in the supine position. Measurements of the pulse rate, respiratory rate, and blood pressure were taken during a control period and repeatedly during the course of each experiment. Arterial blood pressure was recorded by direct intra-arterial manometry. Cerebral blood flow was determined by the nitrous oxide method of Kety and Schmidt. Following the control observations, 50 mg. of chlorpromazine were given intravenously (over a 10-minute period of time) to 7 subjects and intramuscularly to 4 subjects. Two additional subjects received 25 mg. and 60 mg., respectively, by the intravenous route. A second cerebral blood flow determination was made 1 hour after the administration of the drug. The blood pH determinations were done on a Beckman pH meter with a water bath maintained at body temperature. The Van Slyke manometric apparatus was used for the gas analysis, and aerosol was used as the hemolytic agent.

Results

The effects of chlorpromazine (Thorazine)* on cerebral blood flow, mean blood pressure, and cerebral oxygen metabolism are recorded in Table 1. Chlorpromazine usually produced a temporary increase in respiratory rate follow-

* Furnished by Smith, Kline & French Laboratories.
Table 1.—Cerebral Hemodynamic Response to Chlorpromazine (SKF 2601)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean blood pressure</th>
<th>Cerebral blood flow, ml./100 Gm./min.</th>
<th>Cerebrovascular resistance</th>
<th>Cerebral Oxygen uptake</th>
<th>Dose† mg.</th>
<th>Per cent oxygen saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C D C D</td>
<td>C D</td>
<td>C D</td>
<td></td>
<td>Arterial</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C D C D</td>
</tr>
<tr>
<td>1. V.G.</td>
<td>81</td>
<td>69</td>
<td>46 51</td>
<td>1.8 1.4</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>2. A.B.</td>
<td>101</td>
<td>70</td>
<td>40 29</td>
<td>2.5 2.4</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>3. E.L.</td>
<td>103</td>
<td>82</td>
<td>43 35</td>
<td>2.4 2.3</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>4. O.A.</td>
<td>51</td>
<td>76</td>
<td>44 48</td>
<td>1.8 1.6</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>5. N.N.</td>
<td>103</td>
<td>116</td>
<td>65 56</td>
<td>1.6 2.1</td>
<td>4.6</td>
<td>3.4</td>
</tr>
<tr>
<td>6. C.P.</td>
<td>107</td>
<td>86</td>
<td>61 36</td>
<td>1.8 2.4</td>
<td>1.9</td>
<td>2.2</td>
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<tr>
<td>7. F.R.</td>
<td>94</td>
<td>87</td>
<td>38 42</td>
<td>2.5 2.1</td>
<td>4.1</td>
<td>3.9</td>
</tr>
<tr>
<td>8. F.S.</td>
<td>85</td>
<td>63</td>
<td>54 33</td>
<td>1.6 1.9</td>
<td>2.9</td>
<td>1.7</td>
</tr>
<tr>
<td>9. A.S.</td>
<td>101</td>
<td>76</td>
<td>37 38</td>
<td>2.7 2.0</td>
<td>3.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Mean

% of Control 85 85 85 97 90 89

p Value‡ <.01 <.10 <.50 <.50 <.40 <.10

Group B

10. A.L. 78 80 45 45 1.7 1.8 2.8 3.0 50 96 98 59 59
11. E.M. 95 101 35 41 2.7 2.5 2.0 2.5 50 95 88 61 52
12. G.F. 96 92 58 60 1.7 1.5 3.5 3.8 50 97 99 65 66
13. R.T. 98 89 50 54 1.7 1.6 3.0 2.5 50 98 97 67 69

Mean

% of Control 92 91 49 50 2.0 1.9 2.8 3.0 50 97 96 63 62
99 102 95 107 99 98

Group A, intravenous administration.
Group B, intramuscular administration.
C = Control observations
D = Observations 1 hour after the administration of chlorpromazine
* = ml./100 Gm. of brain/min.
† = Dose chlorpromazine
‡ = Statistical analysis by R. A. Seibert: $t = \sqrt{\frac{\sum n(n - 1)}{S^2}}$

ing the intravenous administration of the drug, but, by the time studies of the post drug cerebral blood flow were done, the respiratory rate and depth were similar to the control observations. Also, the pulse rate increased rather significantly immediately after the chlorpromazine administration, but this effect was usually insignificant after 1 hour; however, a moderate increase in pulse rate was sometimes observed at the time of the second determination of cerebral blood flow. The subjects universally showed less apprehension after the administration of chlorpromazine, but only 2 of them (N.N. and F.S.) showed a noticeable degree of somnolence.

There was a reduction in mean blood pressure in all but 1 subject following intravenous administration of the drug ($p < 0.01$). This drop persisted throughout the period of the experiment and usually was evident for 2 or 3 hours. Associated with the reduction in mean blood pressure there was frequently a slight reduction in cerebral blood flow. However, this was a variable response and was not consistent enough to be statistically significant ($p < 0.10$) for the number of subjects* studied. Whenever a marked reduction in cerebral blood flow occurred, it was preceded by an acute reduction in mean blood

* If a larger group of patients had been studied, this value probably would have become statistically significant.
TABLE 2.—Effect of Chlorpromazine on Cerebral Blood Oxygen and Carbon Dioxide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Arterial O2 Volume %</th>
<th>Venous O2 Volume %</th>
<th>Arteriovenous O2 Difference</th>
<th>Arterial CO2 Volume %</th>
<th>Venous CO2 Volume %</th>
<th>Arterial PCO2</th>
<th>Venous PCO2</th>
<th>Hematocrit</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. V.G.</td>
<td>24</td>
<td>♂</td>
<td>14.0</td>
<td>14.0</td>
<td>9.4</td>
<td>8.4</td>
<td>4.6</td>
<td>5.6</td>
<td>48.5</td>
<td>52.0</td>
</tr>
<tr>
<td>2. A.B.</td>
<td>34</td>
<td>♂</td>
<td>18.6</td>
<td>19.3</td>
<td>9.8</td>
<td>7.5</td>
<td>8.8</td>
<td>11.8</td>
<td>43.8</td>
<td>43.6</td>
</tr>
<tr>
<td>3. E.L.</td>
<td>38</td>
<td>♂</td>
<td>18.3</td>
<td>19.0</td>
<td>9.9</td>
<td>7.9</td>
<td>8.4</td>
<td>11.1</td>
<td>38.4</td>
<td>37.3</td>
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<tr>
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<td>21</td>
<td>♂</td>
<td>16.4</td>
<td>15.4</td>
<td>11.0</td>
<td>10.1</td>
<td>5.4</td>
<td>5.3</td>
<td>47.5</td>
<td>50.8</td>
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<tr>
<td>5. N.N.</td>
<td>40</td>
<td>♂</td>
<td>16.9</td>
<td>16.6</td>
<td>9.8</td>
<td>10.6</td>
<td>7.1</td>
<td>6.0</td>
<td>38.3</td>
<td>45.1</td>
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<tr>
<td>6. C.P.</td>
<td>30</td>
<td>♂</td>
<td>14.7</td>
<td>14.7</td>
<td>11.6</td>
<td>8.6</td>
<td>3.1</td>
<td>6.1</td>
<td>50.2</td>
<td>49.8</td>
</tr>
<tr>
<td>7. F.R.</td>
<td>37</td>
<td>♂</td>
<td>20.2</td>
<td>19.5</td>
<td>9.5</td>
<td>10.1</td>
<td>10.7</td>
<td>9.4</td>
<td>43.8</td>
<td>47.0</td>
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<tr>
<td>8. F.S.</td>
<td>28</td>
<td>♂</td>
<td>16.1</td>
<td>15.6</td>
<td>10.8</td>
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<td>5.3</td>
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<tr>
<td>9. A.S.</td>
<td>35</td>
<td>♂</td>
<td>18.1</td>
<td>18.1</td>
<td>9.3</td>
<td>8.4</td>
<td>8.8</td>
<td>9.7</td>
<td>43.9</td>
<td>45.6</td>
</tr>
</tbody>
</table>

Mean

<table>
<thead>
<tr>
<th>% of Control</th>
<th>Arterial O2</th>
<th>Venous O2</th>
<th>Arteriovenous O2</th>
<th>Arterial CO2</th>
<th>Venous CO2</th>
<th>Arterial PCO2</th>
<th>Venous PCO2</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Control</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Mean</td>
<td>17.0</td>
<td>16.9</td>
<td>10.1</td>
<td>9.1</td>
<td>6.9</td>
<td>7.8</td>
<td>44.9</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Group A, intravenous administration.
Group B, intramuscular administration.
C = Control observations
D = Observations made 1 hour after the administration of chlorpromazine.

pressure. The relationship between blood pressure reduction and decreased cerebral blood flow was confirmed by the observations made on the 4 subjects who received the drug intramuscularly, since neither mean blood pressure nor cerebral blood flow decreased in this group.

Despite the slight reduction in cerebral blood flow that was frequently observed following the administration of chlorpromazine intravenously, it was not associated with a reduction in cerebral oxygen uptake (p > 0.50). The mean cerebral oxygen uptake prior to chlorpromazine administration was 3.2 ml./100 Gm. of brain/min. and after drug administration it was 3.1 ml./100 Gm. of brain/min. (97 per cent of control), indicating that cerebral oxygen metabolism was not affected by the administration of chlorpromazine. When the drug was given by the intramuscular route, there was likewise no effect on cerebral oxygen uptake.

Among the significant effects on blood gases was a rather consistent reduction in jugular blood oxygen content (p < 0.05) following intravenous administration of chlorpromazine. This change was frequently associated with an increase in arterial-venous oxygen difference (p < 0.10), probably a reflection of the occasional reduction in cerebral blood flow associated with the mild hypotensive response to chlorpromazine administered intravenously. When the drug was given intramuscularly and the hypotensive effect did not occur, neither the oxygen content of the jugular blood nor the cerebral arterial-venous oxygen difference was affected (table 2).

As the oxygen content of the jugular blood decreased following intravenous administration of chlorpromazine, there was a slight increase...
in venous CO₂ content (p < 0.01) but not in pCO₂. Again, this increase occurred only after intravenous administration and probably reflects the frequent reduction in cerebral blood flow associated with the hypotensive response to the drug. After intramuscular administration there was no significant effect on CO₂ content of the blood, coming from or going to the brain.

**DISCUSSION**

It appears that chlorpromazine has very little direct effect on cerebral blood flow or cerebral oxygen metabolism per se, and the only alterations that occur are those that follow the reduction in blood pressure resulting from the peripheral adrenergic blocking effect of the drug.¹ Figure 1 summarizes a typical response. The reduction in mean blood pressure may or may not be accompanied by a concurrent reduction in cerebral blood flow (table 1). This cerebral hemodynamic response is no different from that observed when other hypotensive agents, such as ganglionic and adrenergic-blocking agents, are given to normotensive individuals and the blood pressure is reduced to hypotensive levels.² ³ For example, in figure 2 is seen the typical hemodynamic response of a normotensive individual given a continuous infusion of hexamethonium.⁴ As the blood pressure decreases to hypotensive levels, cerebral blood flow is reduced concurrently. This change is associated with an increase in the cerebral arteriovenous oxygen difference and a minimal, or no, alteration in oxygen uptake by the brain.

Further support to the blood pressure effect on cerebral blood flow was furnished when the chlorpromazine was given intramuscularly. Under these circumstances the sharp reduction in mean blood pressure was not observed with the subject in the supine position (as was the case in the current experiment). As a result, cerebral blood flow was not reduced and cerebral arteriovenous oxygen difference was not affected. Furthermore, in those subjects whose reduction in cerebral blood flow was associated with a hypotensive response to intravenously administered chlorpromazine, intravenous infusion of norepinephrine brought about a return toward normal in cerebral blood flow (figs. 1 and 3), as the mean blood pressure increased to the control levels. There was no effect on cerebral arteriovenous oxygen difference and no effect on cerebral oxygen uptake (fig. 1) during the infusion of normo-

![Fig. 1. Response to chlorpromazine given intravenously. As the blood pressure decreased, cerebral blood flow decreased without affecting cerebral oxygen uptake. When the arterial blood pressure was then increased with an infusion of norepinephrine, cerebral blood flow also increased.](image)

![Fig. 2. Typical cerebral hemodynamic response to blood pressure reduction employing a continuous infusion of a ganglionic-blocking agent. As the blood pressure decreases, cerebral blood flow is depressed. Cerebral oxygen uptake is not altered unless the reduction in cerebral blood flow becomes marked.](image)
epinephrine if these had not previously been altered by the hypotension associated with chlorpromazine administration. Occasionally a slight depression in cerebral oxygen consumption accompanied the reduction in cerebral blood flow associated with the hypotension due to chlorpromazine administered intravenously. This was an erratic response and was apparently due to insufficient oxygen being extracted from the blood flowing through the brain to compensate for the degree of reduction in cerebral blood flow that accompanied the hypotension. When the blood pressure was returned to control levels in these patients by the infusion of norepinephrine, cerebral oxygen consumption, as well as cerebral blood flow, increased toward normal. Such an example is presented in subject F.S., in whom the reduction in cerebral blood flow was associated with a depression in cerebral oxygen consumption (fig. 3). Both alterations were corrected by increasing the blood pressure to control values with the continuous intravenous infusion of norepinephrine. Similar results were achieved by giving norepinephrine to subjects 2 (A.B.), 6 (C.P.), and 8 (F.S.), who showed a reduction in cerebral blood flow following the administration of chlorpromazine, (figs. 1 and 3). Doses of chlorpromazine up to 300 mg. appear to produce no difference in response from that noted in the current study.\(^7\)

The metabolic effect of chlorpromazine is quite different from that observed with barbiturates and morphine.\(^2\) For example, figure 4 presents a typical response to 60 mg. of morphine given intravenously. The morphine did not affect cerebral blood flow, but did cause a marked reduction in cerebral oxygen uptake. Apparently this results from a general depressant effect on cerebral metabolism. Similar observations have been made following the administration of intravenous pentothal.\(^2\)

**Summary**

The cerebral hemodynamic effects of chlorpromazine administered intravenously and intramuscularly were observed in 13 subjects. Cerebral blood flow was frequently reduced following the intravenous administration of chlorpromazine, but apparently this change was a result of the associated reduction in mean arterial blood pressure, rather than a direct effect of the drug on the cerebral circulation. When the blood pressure was then

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**Fig. 3.** Response to chlorpromazine given intravenously in a subject who showed a marked reduction in mean blood pressure and cerebral blood flow. The increased extraction of oxygen from the cerebral blood was inadequate to prevent a reduction in cerebral oxygen uptake. When the blood pressure was increased to control levels with norepinephrine both cerebral blood flow and cerebral oxygen uptake increased.

**Fig. 4.** Cerebral response to morphine given intravenously. Cerebral oxygen uptake was depressed without affecting mean blood pressure or cerebral blood flow. The process was reversed with N-allylnormorphine [Nalline (NAM)].
elevated to normotensive levels with norepinephrine, the cerebral blood flow returned toward normal. Chlorpromazine did not exert a direct depressant effect on cerebral oxygen consumption. When chlorpromazine was given by the intramuscular route, the blood pressure was not reduced significantly, and cerebral blood flow and cerebral oxygen consumption were not altered. The metabolic effect of chlorpromazine is quite different from that of morphine and barbiturates, since the latter agents depress cerebral oxygen uptake without affecting cerebral blood flow.

SUMMARIO IN INTERLINGUA

Esseva observate in 13 subjectos le effectos cerebro-hemodynamic de chlorpromazina in administrationes intravenose e intramuscular. Le fluxo de sanguine cerebral esseva frequentemente reduceite post le administration intravenose de chlorpromazina, sed il pare que iste alteration esseva le resultato del associate reduction del median pression arterial plus tosto que un effecto directe exercite per le droga super le circulation cerebral. Le re-elevation del pression sanguineae a nivellos de normotensivitatem effectuate per medio de norepinephrina esseva sequite per le renormalisation del fluxo de sanguine cerebral. Chlorpromazina non exerceva un effecto directemente depressive super le consumption cerebral de oxigeno. Quando chlorpromazina esseva administrate intramuscularmente, le pression sanguineae non se reduceva significativamente, e le fluxo de sanguine cerebral e le consumption cerebral de oxigeno non esseva altere. Le effecto metabolic de chlorpromazina es multo differente ab le effecto de morphina e del barbituratos que deprime le acceptation cerebral de oxigeno sin afficer le fluxo de sanguine cerebral.

REFERENCES

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