Effect of tinofedrine (Homburg D8955) on cerebral blood flow in multi-infarct dementia


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SUMMARY Tinofedrine, a new derivative of l-norephedrine, was examined for cerebral vasodilator activity in man. Ten patients with reduced cerebral blood flow (CBF) and multi-infarct dementia were given the drug intravenously. Cerebral blood flow increased significantly by 28% from a mean of 43.3 to 55.5 ml/100 g/min.

The place of cerebral vasodilator drugs in the treatment of dementia is uncertain. The justification for their use has been the hypothesis that there are areas of brain where blood flow fails to meet the metabolic demands. The presence of hypoperfused but histologically normal cerebral tissue has been demonstrated in chronic stroke models (Symon et al., 1975), but their presence in patients with multi-infarct dementia has been disputed (Lenzi et al., 1977). A large number of vasodilators have been tried in cerebrovascular disease (McHenry, 1972; Olesen, 1974; Iliff et al., 1977). In the past the emphasis has been on attempting to improve metabolism and intellectual function by increasing cerebral blood flow (CBF).

Patients with multi-infarct dementia tend to have reduced CBF quite early in the course of the disease, whereas mild cases of dementia caused by primary cerebral degeneration do not (Hachinski et al., 1975). A possible advantage of increasing blood flow, especially in the former group, is that by so doing the chances of further infarction might be reduced. A drug that could be shown to be an effective and non-toxic cerebral vasodilator in man would merit a therapeutic trial in patients with multiple infarcts in order to assess whether further deterioration was prevented.

A new and potent cerebral vasodilator in animals is tinofedrine (D8955 Homburg) (Fig. 1). It is a derivative of l-norephedrine (Fig. 2) with some different pharmacological properties. For example, tinofedrine increases cerebral blood flow much more than l-norephedrine in experimental animals (J. F. Harper, personal communication). Its cardiovascular effects are an increase in cardiac output mainly by an increase in stroke volume with only a slight increase in heart rate. There may be a mild increase in systemic blood pressure and pulmonary arterial pressure. Pulmonary vascular resistance decreases. Side effects are minimal. We considered a trial of its acute administration in man to be worth while.

Methods

Ten patients, six women and four men, were treated. All had multi-infarct dementia according to clinical criteria. Their ages ranged from 52 to
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82 years, with a mean of 66 years. The nature of the investigation was explained to them and their relatives by someone not involved in their management, and consent was obtained.

Cerebral blood flow (CBF) was measured by a non-invasive isotopic clearance technique using the bi-compartmental analysis of Obrist et al. (1975). We injected 5-7 mCi of $^{133}$Xe intravenously and clearance was monitored for 11.5 minutes by six extracranial detectors. The results were expressed as the cerebral blood flows (F₁ and F₂ ml/100 g/min) for the fast- and slow-clearing compartments respectively. The fast-clearing compartment approximates to grey matter and the slow-clearing compartment consists of both white matter and extracerebral tissue. The flow of the fast-clearing compartment was also expressed as a percentage of the total flow of the tissue under observation (FR). Cerebral blood flow was measured before and during an intravenous infusion of tinofedrine. Thirty minutes after the first CBF measurement, an intravenous bolus of 0.15 mg of tinofedrine per kilogram body weight was administered over two minutes. This was immediately followed by a slow intravenous infusion of 5 mg of tinofedrine over the next 20 minutes. The isotope injection for the second CBF measurement was given 10 minutes after the start of the bolus injection.

At the beginning of each CBF measurement, PCO₂ was measured in blood taken without stasis from a vein in the dorsum of the hand which had been heated to 35°C. It has been shown that under these conditions, the venous PCO₂ closely approximates systemic arterial PCO₂ (Brooks and Wynn, 1959). Blood pressure was monitored repeatedly throughout the procedure by a standard sphygmomanometer cuff.

### Results

The mean cerebral blood flows (F₁) obtained from the six extracranial detectors before and during administration of tinofedrine are presented in the Table. In nine out of the 10 patients there was an increase in F₁ during the drug infusion. In only one patient was there a decrease. Initially, the mean F₁ was 43.3 ml/100 g/min (SD 7.3). During treatment the mean F₁ was 55.5 ml/100 g/min (SD 13.7), an increase of 28%. Paired t test analysis showed this increase to be significant ($t=3.49, 0.01<P<0.005$). The mean values of F₂ and FR did not change significantly during the drug infusion.

There was no significant change in PCO₂ before or during tinofedrine administration (37.7 and 38.5 Torr respectively). Also, the mean arterial blood pressure did not change significantly before and during drug administration (108.3 and 110 torr respectively). During CBF measurement, all blood pressures were taken in the supine position. No significant postural effects on blood pressure were noted when the patient stood up after the study. No adverse reactions occurred.

### Discussion

The finding of a significant increase in F₁ in this group of patients given tinofedrine intravenously shows clearly that this drug has a cerebral vasodilator action, at least in the fast-perfusing tissue compartment. No significant changes overall were seen in F₂ which represents flow in the slow-clearing tissue compartment, made up of white matter and extracerebral tissue (Obrist et al., 1975). There was also no significant overall change

### Table: Cerebral blood flow (F₁) and PCO₂ before and during infusion of tinofedrine intravenously

<table>
<thead>
<tr>
<th>Patients</th>
<th>Before infusion</th>
<th>During infusion</th>
<th>Difference</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F₁ (ml/100 g/min)</td>
<td>PCO₂ (Torr)</td>
<td>F₁ (ml/100 g/min)</td>
<td>PCO₂ (Torr)</td>
</tr>
<tr>
<td>1</td>
<td>50.3</td>
<td>37.5</td>
<td>82.7</td>
<td>37.5</td>
</tr>
<tr>
<td>2</td>
<td>40.8</td>
<td>40.5</td>
<td>37.4</td>
<td>39.0</td>
</tr>
<tr>
<td>3</td>
<td>54.2</td>
<td>35.0</td>
<td>56.0</td>
<td>39.5</td>
</tr>
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<td>37.0</td>
<td>41.5</td>
<td>49.0</td>
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</tr>
<tr>
<td>5</td>
<td>40.8</td>
<td>35.0</td>
<td>55.4</td>
<td>33.5</td>
</tr>
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<td>39.7</td>
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<td>7</td>
<td>42.5</td>
<td>35.0</td>
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<td>35.0</td>
</tr>
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<td>37.7</td>
<td>40.0</td>
<td>41.7</td>
<td>40.0</td>
</tr>
<tr>
<td>9</td>
<td>34.9</td>
<td>42.5</td>
<td>42.4</td>
<td>44.0</td>
</tr>
<tr>
<td>10</td>
<td>55.3</td>
<td>37.0</td>
<td>64.1</td>
<td>39.0</td>
</tr>
</tbody>
</table>

Mean 43.3* 37.7† 55.5* 38.5† +12.2 28.0

Mean Standard deviation 43.3 37.7 55.5 38.5 12.2 28.0

* = $t=3.49, 0.01>P>0.005$.
† = Not significant.
in FR, indicating that the compartmental weights remained constant. The action of the tinofedrine to increase $F_1$ was not mediated by changes in PCO$_2$ or arterial blood pressure.

The increases in CBF found in this study may be slightly underestimated. It has been shown that when two CBF measurements are made within an hour of one another under the same conditions, the second $F_1$ is usually a little lower than the first (Palmer et al., 1977). This is probably due to a reduction in the patient's level of anxiety as he becomes accustomed to the test.

It would be interesting to observe the effects of tinofedrine on CBF in patients when taken orally for several weeks. If the improvement in CBF persists a therapeutic trial in multi-infarct dementia would be justified.

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References


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