β-Adrenoreceptor-blocking agents and the blood–brain barrier

J. M. CRUICKSHANK*, G. NEIL-DWYER†, M. M. CAMERON‡ and J. McAINSH*

†Department of Neurosurgery, Brook General Hospital, London, *Imperial Chemical Industries Limited, Pharmaceuticals Division, Macclesfield, Cheshire, and ‡Pinderfields General Hospital, Wakefield, Yorkshire, U.K.

Summary

1. Sixteen neurosurgical patients received (oral) β-adrenoreceptor-blocking agents (β-receptor blockers) for 3–22 days.
2. Lipophilic β-receptor blockers (propranolol) and metoprolol appeared in cerebrospinal fluid at concentrations similar to the free drug plasma concentration.
3. Cerebrospinal fluid concentrations of β-receptor blockers were poor predictors of brain concentrations.
4. Both lipophilic β-receptor blockers appeared in high concentrations in the brain: the brain/plasma ratio was approximately 15:1.
5. Hydrophilic atenolol appeared at low concentrations in brain tissue (about 20 times lower than the lipophilic β-receptor blockers): the brain/plasma ratio was approximately 0.1:1.
6. Central nervous system-related side effects associated mainly with lipophilic β-receptor blockers possibly result from high brain tissue concentrations.

Key words: adrenoreceptor, blood–brain barrier, metoprolol, propranolol.

Introduction

Interest in a possible direct action of β-adrenoreceptor blockers upon the central nervous system has centred around two main areas: (i) as an explanation of their antihypertensive effects, and (ii) as an explanation of some of their side effects. The critical factors which determine penetration of the blood–brain barrier are the lipid/water partition coefficient and protein binding of the β-receptor blocker. The present study was therefore set up to investigate the human central nervous system pharmacokinetics of the following three β-receptor blockers: propranolol, which is highly lipophilic (log octanol/water partition coefficient of 3.65 = log P) and highly plasma protein bound (approximately 90%); atenolol, which is highly hydrophilic (log P = 0.23) and poorly plasma protein bound (approximately 3%); and metoprolol, which is moderately lipophilic (log P = 2.15) and lowly plasma protein bound (approximately 10%).

Patients and methods

The study was in two sections.

(1) Nine patients (eight with a subarachnoid haemorrhage at least 1 week before and one with back pain) received β-receptor blocker therapy for 5–11 days (Table 1) before lumbar puncture. Two hours after the last tablet, a blood sample was taken and then a lumbar puncture was performed for cerebrospinal fluid collection. Propranolol concentration was estimated according to the gas–liquid chromatography method (McAinsh, Baber, Smith & Young, 1978), and atenolol and metoprolol (Hazleton Laboratories, Harrogate) concentrations were estimated according to an amended method of Scales & Copsey (1975). Three of the patients had received propranolol, 80 mg twice daily, three atenolol, 100 mg once daily, and three metoprolol, 100 mg twice daily.

(2) Seven patients (five with either anterior or middle cerebral arterial aneurysms and two with chronic depression/anxiety requiring stereotactic tractotomy) received the β-receptor blocker for 3–22 days (Table 1) before surgery. Three received propranolol, 80 mg twice daily, three atenolol, 100 mg once daily, and another one metoprolol, 100 mg twice daily. Last tablets were given 1–10 h (Table 1) pre-operatively. At
operation, in order to display aneurysms, small portions of brain (frontal or temporal cortex) were removed. Before stereotactic tractotomy, a routine frontal cortical biopsy was performed. The samples were wiped with a dry gauze and immediately deep-frozen. At the same time, a cerebrospinal fluid and a blood (plasma) sample were taken. These samples were put immediately into deep-freeze at -20°C. In the case of metoprolol, the blood was centrifuged.

### Results

#### Study 1

Atenolol (which is virtually non-metabolized) appeared in a higher concentration in the blood than the other two \(\beta\)-receptor blockers. Propranolol was only just detectable in the cerebrospinal fluid, whereas the other two agents were present in concentrations more than ten times those of propranolol. The blood/cerebrospinal fluid ratio was approximately 17:1 for propranolol, 10:1 for atenolol and 1:1 for metoprolol.

#### Study 2

The plasma and cerebrospinal fluid results were broadly similar to those in study 1 (Table 1).

Both lipophilic \(\beta\)-receptor blockers appeared in high concentration in the brain, being about 20 times the concentration of hydrophilic atenolol. Brain concentrations of atenolol were remarkably constant, irrespective of either timing of last dose or blood concentration. The brain/plasma ratios were approximately 17:1 for propranolol, 14:1 for metoprolol and 0:1:1 for atenolol. The brain/cerebrospinal fluid ratios were approximately 17:1 for propranolol, 16:1 for metoprolol and 2:1:1 for atenolol.

#### Discussion

The free \(\beta\)-receptor blockers in the plasma should equilibrate with both the bound drug in the plasma and the free drug in the cerebrospinal fluid and brain: the free drug in the cerebrospinal fluid and brain should equilibrate with bound drug in the cerebrospinal fluid and brain. This equilibration has been shown to be rapid for lipophilic propranolol (Myers, Lewis, Reid & Dollery, 1975) and metoprolol (van Zwieten & Timmermans, 1979). Hydrophilic \(\beta\)-receptor blockers equilibrate much more slowly (Scales & Cosgrove, 1972; van Zwieten & Timmermans, 1979). The cerebrospinal fluid levels of both propranolol and metoprolol in the present study were roughly equivalent to the free drug concentration in the plasma (10% or less of plasma.

---

### Table 1. Concentration of \(\beta\)-receptor-blocking agents after chronic oral administration in blood (plasma), cerebrospinal fluid and brain

<table>
<thead>
<tr>
<th>Dose</th>
<th>No.of patients</th>
<th>Time on drug (days)</th>
<th>Pre-operative dose time (h)</th>
<th>Plasma concn. (ng/ml)</th>
<th>Cerebrospinal fluid concn. (ng/ml)</th>
<th>Brain concn. (ng/ml)</th>
<th>Mean plasma/cerebrospinal fluid ratio</th>
<th>Mean brain/plasma ratio</th>
<th>Mean brain/cerebrospinal fluid ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>336</td>
<td>9*</td>
<td>Not done</td>
<td>17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(80 mg twice daily)</td>
<td>5</td>
<td>8</td>
<td>2</td>
<td>204</td>
<td>16</td>
<td>12</td>
<td>Not done</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3</td>
<td>10</td>
<td>2</td>
<td>140</td>
<td>150</td>
<td>163</td>
<td>Not done</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>(100 mg twice daily)</td>
<td>1</td>
<td>12</td>
<td>2</td>
<td>90</td>
<td>150</td>
<td>163</td>
<td>Not done</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Atenolol</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>1800</td>
<td>220</td>
<td>260</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(100 mg once daily)</td>
<td>3</td>
<td>10</td>
<td>2</td>
<td>1330</td>
<td>135</td>
<td>127</td>
<td>Not done</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>9</td>
<td>11</td>
<td>10</td>
<td>17</td>
<td>72</td>
<td>153</td>
<td>3*</td>
<td>15</td>
<td>1183</td>
</tr>
<tr>
<td>(80 mg twice daily)</td>
<td>11</td>
<td>14</td>
<td>10</td>
<td>370</td>
<td>130</td>
<td>130</td>
<td>38</td>
<td>130</td>
<td>2108</td>
</tr>
<tr>
<td>(100 mg twice daily)</td>
<td>1</td>
<td>22</td>
<td>4</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>38</td>
<td>150</td>
<td>2108</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1</td>
<td>10</td>
<td>10</td>
<td>500</td>
<td>72</td>
<td>72</td>
<td>100</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>(100 mg once daily)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>300</td>
<td>40</td>
<td>66</td>
<td>140</td>
<td>40</td>
<td>143</td>
</tr>
<tr>
<td>Atenolol</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2200</td>
<td>85</td>
<td>85</td>
<td>160</td>
<td>160</td>
<td>—</td>
</tr>
</tbody>
</table>

* Not significantly different from zero.
level for propranolol and about 90% of plasma level for metoprolol). The high brain concentration of both propranolol and metoprolol relative to both cerebrospinal fluid and blood levels reflected the high affinity of brain tissue for these lipophilic agents. In contrast to the rapid equilibration of propranolol and metoprolol, where peak free plasma levels will be reflected across the blood–brain barrier, atenolol's speed of equilibration is slow.

As the cerebrospinal fluid in man is completely changed about every 10 h, atenolol's concentration may be kept low by means of a continual washout or sink effect (Davson, 1976). Indeed the cerebrospinal fluid and brain concentrations seem to settle at about one-fifth to one-tenth of peak blood levels (which occur 2–4 h after dosing). Thus, effectively, the brain is buffered against peak plasma levels of atenolol. This might be clinically important as two patients showing psychiatric symptoms on propranolol became well on switching to atenolol (Fraser & Carr, 1976) and 58 out of 63 patients with central nervous system side effects on lipophilic β-receptor blockers (Mattisson & Henningsen, 1978) markedly benefited from a switch to atenolol.

From these data it is still possible that β-receptor blockers have an antihypertensive action mediated through the central nervous system. Atenolol may be present in other parts of the brain (e.g. pons–medulla) in much higher concentrations; however, Myers et al. (1975) showed that in man propranolol was evenly distributed throughout all areas in the brain. In any case, the relatively low brain concentration of atenolol might be more than sufficient to cause a fall in blood pressure. However, van Zwieten & Timmermans (1979) showed recently that after intravenous atenolol the maximal fall in blood pressure occurred at a time when no atenolol could be detected in the brain (both total and medullo–pontine).

Acknowledgments

We thank Professor C. T. Dollery for his help and advice and Halzleton Laboratories for the metoprolol estimations.

References


