The Effect of Chronic Propranolol Therapy on Regional Cerebral Blood Flow in Hypertensive Patients

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SUMMARY In 31 hypertensive patients the effect of chronic oral administration of the beta blocking agent propranolol on regional cerebral blood flow (rCBF) was studied, using the non-invasive 133Xenon inhalation technique. The results of the measurements were compared to the rCBF obtained in an age-matched normal control group. Our study shows that during long-term therapy with low doses of propranolol (< 120 mg/daily) the rCBF is unaffected, but it is increased significantly if higher doses (> 120 mg/daily) are used. In all six patients who served as their own control, as they had basic rCBF measurements before or during low-dose propranolol, the rCBF on high-dose propranolol became significantly increased. The possible mechanisms which may cause the increased rCBF on high-dose propranolol are discussed.

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IT HAS BEEN SHOWN that the cerebral vessels are supplied by norepinephrine-containing nerve fibers1-7 and there is also evidence for the presence of alpha and beta adrenergic receptors in the micro-vessels of the brain.8-10 Alpha adrenergic receptor stimulation or blockage was shown to decrease or increase, respectively, the cerebral blood flow (CBF),11-14 but the effect of the pharmacological manipulation of the beta receptors on the CBF is not well established. Stimulation of these receptors with isoproterenol was shown by some authors to have no effect15 and by others to increase16-17 CBF, while beta blockade, mainly by propranolol, produced either no effect15-18 or a decrease19-23 in CBF in experimental animals and in humans.

In spite of the wide use of beta blocking agents in the management of patients with hypertension, very little data is available on the effect of these drugs on the human cerebral circulation. If chronic beta blockade is associated with a reduction in the CBF, as it was shown by the above quoted investigators in acute studies,19-23 this drug could become potentially harmful for hypertensive patients and perhaps may even increase the risk of cerebral ischemia. Therefore, in this study we measured CBF in hypertensive subjects treated chronically with various doses of propranolol and compared the results with the CBF measured in a normotensive untreated age-matched control group.

Patients and Methods

Thirty-one ambulatory patients with essential hypertension were included in this study. Each patient gave his agreement and consent for participating in the study according to its protocol, after the explanatory details were given. The patients were free from neurological, hepatic, renal, pulmonary or other clinical conditions, as established by meticulous medical history. Physical examination and laboratory tests were within the normal limit including PCO2 and hemoglobin values. Hypertension was defined if the mean of three separate measurements of the diastolic pressure was 100 mm Hg or higher. At the beginning of the study 27 patients were already on prolonged propranolol treatment and CBF was measured with the below described method, on two different occasions within 1-4 weeks during the therapy. In two of these patients, the dosage was increased after the first set of CBF measurements and the study was repeated while the patient received the higher dosage. Four other patients had no previous treatment and after basic rCBF measurement, propranolol was started and after one month of treatment, rCBF was repeated. In none of the patients was a significant change in blood pressure observed between the two CBF measurements. No other drug but propranolol was given to any of the patients during the study period.

The regional CBF (rCBF) was measured by the 133Xenon inhalation technique developed and described in detail by Obrist et al24,25 and used by us in previous studies.26 Briefly, the study was conducted in the resting relaxed state, in a darkened room with the patient lying on a bed with plugged ears and closed eyes. After adjustment to the apparatus, 133Xenon mixed with air (2.5 mCi/l) was inhaled for one minute through a close-fitting face mask and a non-rebreathing system. The clearance of 133Xenon from the brain was recorded for 10 minutes by 8 pairs of NaI collimated scintillation detectors incorporated into an on-line computerised system and applied externally over homologous regions of the skull with the head relating to the probes in a standard position. The concentration of the radioisotope in the expired air, sampled by a thin catheter ending in the face mask and connected to a vacuum pump, was monitored by a separate detector. The end-tidal concentration of the 133Xenon in the expired air made an “air curve” which was used to correct the “head curves” for recirculation of the inhaled radioisotope. The rCBF was computed for each “head curve” as the Initial Slope Index (ISI), derived

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from the initial slope of the clearance curves between the second and third minutes. Blood brain partition coefficient of $^{133}$Xenon was arbitrarily chosen as 1 and ISI data are presented in ml/100 g/min units. The ISI values obtained in our patients were compared with those obtained in a series of 101 healthy, non-hospitalized normotensive control subjects aged 38 to 70 years (mean 53.6). The control values were used to obtain the age-matched expected rCBF, i.e., the expected rCBF values for each patient according to age.

**Results**

The 31 patients included in this study were divided according to the daily dose of propranolol intake (table 1). Group 1 included those 20 patients who received 40-100 mg propranolol daily and Group 2 included those 13 patients who received 120-200 mg propranolol daily. There were 12 males and 8 females, aged 44 to 76 years (mean age 59.1 years) in Group 1 and 6 males and 7 females, aged 39 to 72 years (mean age 59.4 years) in Group 2. The mean arterial blood pressure at the time of the study in Group 2 was slightly higher than in Group 1, but this difference was statistically non-significant (table 2). No differences were found between the rCBF measured in the patients receiving low-dose propranolol (Group 1) and the expected age-matched control. However, a significant increase, by 19.6%, in rCBF was found in the group of patients receiving propranolol 120 mg/day or more (Group 2) as compared to the expected age-matched rCBF (table 2). The increase in rCBF during chronic high-dose propranolol therapy was demonstrated also in six of our patients who served as controls of themselves: four of these patients received no therapy at the time of entering the study and two others received 40 mg propranolol daily. All six had rCBF values almost identical to the expected values while on chronic low-dose propranolol and in all patients propranolol 120-

**Discussion**

Our results show that the chronic administration of high-dose propranolol (more than 120 mg/day) increases rCBF whereas a relatively lower dose has no such effect. These findings are different from those reported by Griffith et al who found that the rCBF in hypertensive patients remained unaltered not only during administration of low doses of beta blocking agents but also in those who received high doses. Acute administration of these drugs was demonstrated to reduce rCBF in hypertensive patients by Hares et al, an effect not observed by either Griffith and associates or by us during chronic propranolol therapy. The cause for the increase in rCBF during chronic administration of high-dose propranolol is not clear. It is unlikely that this effect is due to the specific blockade of beta adrenergic receptors by propranolol in the cerebral vessels, since in this case one would expect a similar change, possibly to a lesser degree, also in the group who received the low-dose propranolol. There is a possibility that chronic high-dose propranolol en-

**Table 1. Effects of Chronic Propranolol Therapy on rCBF in Hypertensive Patients**

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>40-110 mg/d</td>
<td>120-200 mg/d</td>
</tr>
<tr>
<td>Patients</td>
<td>No. 20</td>
<td>No. 13</td>
</tr>
<tr>
<td>M</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>F</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Age</td>
<td>44-76 years</td>
<td>39-72 years</td>
</tr>
<tr>
<td>mean</td>
<td>59.1 years</td>
<td>59.4 years</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Propranolol Dose on Blood Pressure and rCBF**

<table>
<thead>
<tr>
<th></th>
<th>Mean Blood Pressure (mmHg)</th>
<th>Mean rCBF (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Group I — propranolol (40-110 mg/d)</td>
<td>149.5 ± 27.9</td>
<td>85.3 ± 9.0</td>
</tr>
<tr>
<td>Group II — propranolol (120-200 mg/d)</td>
<td>168.5 ± 36.8</td>
<td>92.4 ± 13.7</td>
</tr>
</tbody>
</table>

± S.D.

*p < 0.01 Measured vs. expected flow.
hances brain neuronal metabolism and secondarily increases the rCBF. Or else, propranolol is known to have a direct "quinidine-like" effect on the smooth muscle in the peripheral vasculature, which reduces the excitability of the smooth muscle fibers in the blood vessels, causing vasodilatation; perhaps chronic high dose propranolol may have a similar direct vasodilating effect on cerebral blood vessels. Six of our patients had both a control rCBF measurement (without propranolol or on low-dose propranolol) and a second measurement on high-dose propranolol; although no patient showed a change in systemic blood pressure between the two measurements, the second test demonstrated a higher rCBF. This provides proof for the assumption that a decrease in the cerebrovascular resistance due to the high-dose propranolol must have induced the increase in rCBF. The cerebrovascular resistance in patients with untreated hypertension is most probably increased, which helps to maintain a normal rCBF in the presence of the increased systemic pressure. This high resistance seems to be unaltered by the low-dose propranolol (our Group 1) or by methyldopa.

The clinical significance of a chronically decreased cerebrovascular resistance in patients on high-dose propranolol and the consequent permanent increase in flow, is not clear. It has generally been accepted to look upon the initiation of a vigorous hypotensive therapy as being dangerous to the patient as sudden decrease in blood pressure can be followed by a sudden reduction in rCBF resulting in syncope or even ischemic brain damage; this has usually been described to follow methyldopa therapy, but not the administration of propranolol. This is compatible with the results of our study with chronic propranolol treatment which shows a long-term increase in rCBF while receiving this drug, and as mentioned above, this is best explained by a local vasodilating effect of this drug on the cerebral circulation. However, there is a possibility that the chronic increase in rCBF during prolonged propranolol treatment may not exclusively be beneficial, as a hyperfusion of the brain may be followed by congestion of the brain vessels which under certain circumstances can culminate in brain edema and in the clinical condition of hypertensive encephalopathy. Furthermore, an increased rCBF may be a precipitating factor for hemorrhage, which is usually considered if a hypertensive patient develops stroke. Whether the incidence of strokes in hypertensive patients is influenced by long-term therapy with high-dose propranolol can be determined only by a long-term follow-up of a large number of patients.

References
A 44-year-old woman was found unresponsive at her home. Her blood pressure was unobtainable and respirations were irregular and shallow. She had a past history of epilepsy and had been under treatment with phenytoin 300 mg and phenobarbital 45 mg daily for many years through her family physician. She had also taken chlorpromazine 75 mg daily for a chronic schizophreniform illness. From the circumstances of her discovery, and the clinical observation of early gangrene in one upper extremity it was deduced that she had lain unresponsive for many hours, possibly several days in all. On arrival to a local Emergency Room, treatment for presumed drug overdose was instituted including endotracheal intubation and assisted ventilation. Physical examination revealed a brachial blood pressure of 60/40 mm Hg, pulse rate 32 per minute, rectal temperature 29°C. She was unresponsive to sound, or painful stimulation. There was a superficial pressure sore on the left hip, and gangrene of the left hand. She had spontaneous, nonrhythmic eyelid blinking, random and conjugate roving eye movements laterally, and pupils which were equal, mid-position, round and unreactive bilaterally. Corneal stimulation elicited reflex blinking. The neck was supple. Extremities were flaccid to passive movements and all deep tendon reflexes were absent. Plantar responses were unelicitable. Toxicology studies demonstrated the presence of chlorpromazine and phenytoin in therapeutic levels, and phenobarbital at a toxic level (72 μg/ml). Other laboratory abnormalities on admission included a glucose of 560 mg/dl, BUN 42 units, Creatinine 3.4 mg/dl, Creatine phosphokinase 2288 units. The platelet count was reduced to 86000/mm³. Despite aggressive treatment with intravenous fluids and Dopamine, and correction of hypothermia, she remained hypotensive for the first three days of hospitalization. With institution of hemodialysis, the barbiturate level fell to 22 μg/ml, with no significant improvement in her condition. She re-

Symmetric Brainstem Necrosis in an Adult Following Hypotension: An Arterial End-Zone Infarct?

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SUMMARY A 44-year-old woman with prolonged coma and hypotension following drug overdose developed bilateral hemorrhagic infarcts in the dorsolateral brainstem. The regional distribution of these paired lesions corresponds to the area of confluence of penetrating arteries in the brainstem. It is suggested that under exceptional circumstances brainstem arterial end-zones may be vulnerable to anoxic-ischemic insult.

THE STRUCTURAL ALTERATIONS of cerebrum and cerebellum following anoxia-ischemia have been studied extensively in man and in experimental animals.1-5 Selective vulnerability of particular regions within the cerebellum and cerebrum has been attributed in part to vascular anatomic factors such as arterial boundary or end-zone distributions. In contrast, studies of the topography of anoxic-ischemic involvement in the brainstem suggest that lesions are topistic; i.e., selective for specific neuronal structures.6-9 This pattern of selective vulnerability in brainstem has been attributed to metabolic factors such as the higher blood flow and metabolic requirements of these nuclei10 and their high level of lactic acid content during anoxia.11 The influence of vascular anatomic factors in the distribution of anoxic-ischemic lesions in brainstem has been given little attention.

A patient with bilateral symmetric columnar necrosis of the brainstem associated with prolonged hypotension is reported. Evidence implicating vascular anatomic factors in the pathogenesis of these brainstem lesions is reviewed.

Case Report

A 44-year-old woman was found unresponsive at her home. Her blood pressure was unobtainable and respirations were irregular and shallow. She had a past history of epilepsy and had been under treatment with phenytoin 300 mg and phenobarbital 45 mg daily for the past many years through her family physician. She had also taken chlorpromazine 75 mg daily for a chronic schizophreniform illness. From the circumstances of her discovery, and the clinical observation of early gangrene in one upper extremity it was deduced that she had lain unresponsive for many hours, possibly several days in all. On arrival to a local Emergency Room, treatment for presumed drug overdose was instituted including endotracheal intubation and assisted ventilation. Physical examination revealed a brachial blood pressure of 60/40 mm Hg, pulse rate 32 per minute, rectal temperature 29°C. She was unresponsive to sound, or painful stimulation. There was a superficial pressure sore on the left hip, and gangrene of the left hand. She had spontaneous, nonrhythmic eyelid blinking, random and conjugate roving eye movements laterally, and pupils which were equal, mid-position, round and unreactive bilaterally. Corneal stimulation elicited reflex blinking. The neck was supple. Extremities were flaccid to passive movements and all deep tendon reflexes were absent. Plantar responses were unelicitable. Toxicology studies demonstrated the presence of chlorpromazine and phenytoin in therapeutic levels, and phenobarbital at a toxic level (72 μg/ml). Other laboratory abnormalities on admission included a glucose of 560 mg/dl, BUN 42 units, Creatinine 3.4 mg/dl, Creatine phosphokinase 2288 units. The platelet count was reduced to 86000/mm³, the PTT was 77 sec., and PT 19.7 sec., consistent with a consumption coagulopathy. A cerebral CT scan was within normal limits. Despite aggressive treatment with intravenous fluids and Dopamine, and correction of hypothermia, she remained hypotensive for the first three days of hospitalization. With institution of hemodialysis, the barbiturate level fell to 22 μg/ml, with no significant improvement in her condition. She re-

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