Propranolol Treatment of Resistant Arterial Hypertension in Patients on Chronic Dialysis

Q MAGGIORE, M BIAGINI, C ZOCCALI, M MISEFARI
Ospedali Riuniti, Reggio Calabria, Italy

Introduction

Bilateral nephrectomy is currently considered as the sole available way of controlling the hypertension of uraemic patients who are not responsive to regular dialysis treatment (RDT), and conventional anti-hypertensive drugs. However, the introduction of new anti-hypertensive agents has opened new perspectives for the pharmacological control of hypertension previously considered intractable. Among the new agents propranolol seems to be of particular interest for its suppressing effect on renin secretion (Winer et al, 1969; Michelakis and McAllister, 1972).

Our investigation was aimed at assessing the efficacy of long-term propranolol administration in patients with arterial hypertension resistant to regular dialysis treatment.

PATIENTS AND METHODS

The eight patients of this study were selected from a population of 54 on regular thrice-weekly dialysis treatment. The selection was based on the presence of arterial hypertension not responsive to ultrafiltration and sodium restriction such as to achieve and maintain dry body weight. Dry body weight was defined as the weight at which the patients had no clinical signs of sodium retention and further ultrafiltration resulted in transient hypotension (Vertes et al, 1969).

Five-hour thrice-weekly haemodialysis was performed, employing the hollow-fibre artificial kidney, in seven patients, and the twin-coil SP75 DASCO cartridge in one. Dialysate sodium concentration was 138 mEq/l. Sodium dietary intake was restricted to 20–40 mEq/day.

The severity of hypertension in these patients was indicated by supine diastolic pressure above 120 mm Hg in the intervals between dialyses, grade 3 to 4.
hypertensive retinal changes, and hypertensive cardiomyopathy as judged by clinical examination, electrocardiogram and chest X-rays.

Six patients had been undergoing dialysis for 3 to 23 months (average 10.2 months) before propranolol treatment was begun. During this period of observation, attempts to control blood pressure with anti-hypertensive drugs including methyldopa, clonidine, and hydralazine, were unsuccessful. Anti-hypertensive drugs were stopped at least two weeks before the beginning of propranolol administration. In two patients propranolol administration was started simultaneously with RDT because their clinical condition appeared so critical that a drug-free control period was deemed not justifiable.

Peripheral plasma-renin activity was assessed by radioimmunoassay according to the Haber method. Angiotensin I, I²⁵I Angiotensin I, and antibody to angiotensin I were obtained from Sorin laboratories. Normal value for PRA obtained from eight normal subjects on a 20–80 mEq sodium diet ranged from 0.4 to 2.8 ng/ml/hr (mean 1.38 ± 0.25 ng/ml/hr). Reproducibility of the procedure, assessed by analysis of variance according to Amenta (1968), was 10.6% between the assays and 5.1% within the assay.

Blood samples were collected between 08.00 and 11.00 of the day following the dialysis, one hour after the patient had lain supine. At least two separate determinations were made in each patient, both during the drug-free period and during propranolol treatment.

Blood pressure was measured by a standard mercury sphygmomanometer both in the supine and erect position at the time of each sampling for PRA determination. On each occasion heart rates were also taken.

Each patient had monthly clinical examination, chest roentgenogram, ECG and fundi examination. In the first 12 months of this trial propranolol was given in association with clonidine (0.3 mg/day). This drug was then withdrawn without observing any variation in the results.

RESULTS

Propranolol treatment in the dosage ranging from 160 to 480 mg/day brought about a fall toward normal tension levels, in both systolic and diastolic blood pressure, in all the eight patients. The response was usually very rapid, being observed within 24–96 hr from the beginning of the administration. The response was sustained through the whole period of observation which, at the present time, ranges from 8 to 18 months (average 13.2 months) (Figure 1). There was no orthostatic hypotension, as shown by the lack of any significant difference between values obtained in the erect and in the supine posture.

Since dialysis treatment may bring the hypertension under control after prolonged periods of time, in some instances after eight months (Comty et al, 1966;
Vertes et al, 1969), we checked the compliance of blood pressure with drug treatment in each patient at least twice, at intervals of 3–6 months, in the course of drug therapy. In each instance propranolol withdrawal resulted in a rapid rise of blood pressure which reached, in 1–17 days, levels comparable to those observed in the pre-treatment period (Figure 2).

Upon drug withdrawal, episodes of angina pectoris recurred in one patient; two patients complained of breathlessness.

The full anti-hypertensive effect was reproduced in all patients when propranolol was given again at the previous dosage.

Variation in funduscopic changes and cardiothoracic index during treatment are given in Table I. There was a marked improvement in funduscopic changes; on


<table>
<thead>
<tr>
<th>Patient</th>
<th>Cardiothoracic Index</th>
<th>Retinal Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>PA</td>
<td>0.58</td>
<td>0.60</td>
</tr>
<tr>
<td>LF</td>
<td>0.44</td>
<td>0.41</td>
</tr>
<tr>
<td>CF</td>
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<td>0.47</td>
<td>0.54</td>
</tr>
<tr>
<td>PT</td>
<td>0.68</td>
<td>0.60</td>
</tr>
<tr>
<td>FA</td>
<td>0.50</td>
<td>0.52</td>
</tr>
<tr>
<td>MS</td>
<td>0.52</td>
<td>0.51</td>
</tr>
<tr>
<td>GR</td>
<td>0.48</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Mean ± SD

0.51 ± 0.07 0.52 ± 0.02

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**Figure 3. Effects of propranolol withdrawal.**

On the other hand, the average cardiothoracic index did not vary significantly. All patients reported improved clinical conditions during propranolol treatment and have resumed their habitual working activity.

The effect of propranolol treatment on plasma-renin activity was assessed by comparing values obtained during and after drug therapy. Figure 3 shows the effect of propranolol withdrawal on diastolic pressure, plasma-renin activity, and heart rate. Figures indicated by columns on the right were obtained 2–11 days...
after propranolol withdrawal, when blood pressure had approached pre-treatment values (n = 13). Figures indicated by columns on the left refer to values obtained during treatment (n = 35). It is seen that propranolol withdrawal results in a significant increase in plasma-renin activity, diastolic blood pressure and heart rate, while average body weight does not vary significantly.

The degree of renin suppression during propranolol treatment was, on the average, 42.5%, plasma-renin activity remaining on levels well above the normal values. On the other hand, plasma-renin activity during treatment was on levels significantly higher (p < 0.05) than that observed in 20 normal-tensive uraemic patients under regular dialysis treatment (PRA = 4.03 ± 2.27 SD).

The effect of treatment on blood pressure does not correlate significantly with the effect on plasma-renin activity (r = 0.34), nor with its logarithm (r = 0.07).

**DISCUSSION**

Patients in this study were considered representative of that small group of the uraemic population on RDT whose hypertension cannot be controlled by sodium-water depletion.

Propranolol administration brought about an excellent control of blood pressure which was sustained up to 18 months. The response was rapid and was associated with very little or no ill-effect. No bradycardia or heart failure occurred.

Beta-blockers have been tried extensively in the treatment of hypertension. However, the degree of their anti-hypertensive effect has been variable, some authors having observed effective control of hypertension (Prichard and Gillam, 1969; Zacharias et al, 1972), while others have found minimal or moderate reduction (Frohlich et al, 1968). There are indications that the magnitude of anti-hypertensive response depends on the type of hypertension, being maximal in those with high plasma-renin activity and lowest in essential hypertension with low PRA (Bühler et al, 1972). The results we obtained in hypertensive uraemic patients with high plasma-renin activity substantiate the belief that high-renin hypertensive patients are peculiarly responsive to the anti-hypertensive action of propranolol. Although a significant hyporeninaemic effect of the treatment has been documented in our uraemic patients, we could not confirm a relationship between the hypotensive and the hyporeninaemic response.

Previous studies on patients with essential hypertension (Frohlich et al, 1968; Frohlich, 1972) have shown that propranolol lowers cardiac output, mainly by reducing heart rate, peripheral resistance being increased or unaffected. From these and other data it has been inferred that this form of treatment may be dangerous as a consequence of its depressant effect on myocardial contractility. The haemodynamic effect of propranolol treatment in hypertensive uraemics is under current investigation in our Unit. The preliminary results of this study show that, after propranolol withdrawal the systemic peripheral resistance increases with the
increase in mean pressure, cardiac output remains unaffected or tends to decrease despite the increase in heart rate, while stroke volume increases.

The haemodynamic effects of propranolol in these patients were opposite to those one would expect from beta adrenergic blockade, a fact which suggests that they are not related to the beta adrenergic blocking action of the drug. A more plausible explanation would seem to be that the anti-hypertensive activity of propranolol is related to its interference with some mediator of vasoconstriction. Further studies are needed to clarify whether or not the mediator of vasoconstriction interfered with by the drug is the angiotensin.

References

Amenta, J S (1968) American Journal of Clinical Pathology, 49, 842

Open Discussion

R KLUTHE Was it necessary to stop therapy? Have you any observations that there is accumulation of the drug, because we know little of the pharmacokinetics and pharmacodynamics of propranolol?
MAGGIORE Thompson et al studied the half-life of propranolol in patients with impaired renal function and normals, and found that the active form of the drug has the same half-life in both. We measured the propranolol level in our uremic patients and found an average level of 114 nanograms/ml four hours after oral administration. 48 hr after stopping the drug the levels were negligible.
KLUTHE And no clinical signs of drug toxicity?
MAGGIORE Only in one patient on one occasion was there looseness of the stool. After reduction of the dosage it disappeared. The drug was then given again in the previous dosage without any side effects. The dose was 480 mg.
KLUTHE What was the sodium concentration in the dialysate?
MAGGIORE 138 mEq/l. They all had high-renin hypertension unresponsive to volume regulation alone.
HURWICH Do you think that from factors such as potassium levels, blood volume, you had evidence that the patients were 'dry'? If they were this would stimulate renin production.

MAGGIORE Since the renin determination was always done 24 hr after dialysis, body weight did not vary. We found no relation between the hyporeninaemic effect and the hypotensive effect of propranolol, but we intend to study the effect of the drug on the metabolic clearance rate of angiotensin II.