**β-Receptor-blockade hypotension and the central nervous system**

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**Summary**

1. Intravenous infusion of propranolol (3.86 μmol h⁻¹ kg⁻¹) for 2 h lowered arterial pressure in the conscious rabbit whereas similar infusions of practolol (37.6 μmol h⁻¹ kg⁻¹) did not.

2. The fall in blood pressure produced by propranolol was accompanied by a decrease in splanchnic nerve activity. Practolol did not change splanchnic nerve activity.

3. A centrally mediated decrease in sympathetic nervous activity makes an important contribution to the hypotensive action of propranolol in the rabbit. This effect is not shown by practolol.

Key words: anti-hypertensive drugs, practolol, propranolol, splanchnic nerve activity.

**Introduction**

The rational development of new anti-hypertensive drugs with β-receptor-blocking activity has been hindered by ignorance of the essential action of β-receptor blockers in hypertensive man. Experimental models of the anti-hypertensive effect are largely unsatisfactory; propranolol is not an effective anti-hypertensive agent in many species even when given for prolonged periods (Farmer & Levy, 1968). However, the rabbit responds to β-receptor blockade similarly to man (Weber, Thornell & Stokes, 1974), having little peripheral β-adrenoreceptor-mediated vasodilator tone.

A method of recording sympathetic nerve activity in the conscious rabbit has recently been developed (Haeusler & Lewis, 1976) and in this report the technique has been used to analyse the relative contribution of central nervous and peripherally mediated hypotensive effects of two β-receptor blockers in the rabbit. Propranolol is a non-selective lipid-soluble drug which is known to be capable of exerting central effects; practolol is a polar cardio-selective drug which is known not to penetrate the brain to any great extent.

**Methods**

New Zealand White rabbits (2–3 kg) were anaesthetized with halothane and the right greater splanchnic nerve was exposed through a laparotomy incision. The nerve was transfixed by two prongs of a bipolar electrode, which was then fixed in position with acrylic dental cement. Flexible wires from the electrode were brought out on to the skin of the back and coiled in a small plastic pouch fixed to the skin.

After a recovery period of 1 week the central artery of an ear was catheterized under local anaesthesia and used for arterial pressure measurement. A venous catheter was inserted into a lateral ear vein.

The conscious animal was then placed in a small wooden box and continuous records of arterial pressure and splanchnic nerve activity were made. Nerve recordings were made with a low level D.C. pre-amplifier and oscilloscope and integrated activity was then derived electronically from the amplified signal.

In all experiments a recovery period of 1 h was followed by a control measurement period of 1 h followed by intravenous infusion of drug for 2 h. All results were expressed as percentage change from control values, all measurements being made by planimetry of the entire record. The drugs studied were propranolol, 3.86 μmol h⁻¹ kg⁻¹ (1 mg h⁻¹...
TABLE 1. Changes in mean arterial pressure and splanchnic nerve activity after control, propranolol and practolol infusion

Results are expressed as mean percentage changes ± SEM from control values. ** P<0.01; * P<0.05.

<table>
<thead>
<tr>
<th>Change (%)</th>
<th>NaCl</th>
<th>Propranolol</th>
<th>Practolol</th>
</tr>
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<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>-1 ± 3</td>
<td>-13 ± 2**</td>
<td>-7 ± 5</td>
</tr>
<tr>
<td>Splanchnic nerve activity</td>
<td>+4 ± 16</td>
<td>-48 ± 9*</td>
<td>+34 ± 28</td>
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</table>

kg⁻¹) and practolol, 37.6 µmol h⁻¹ kg⁻¹ (10 mg h⁻¹ kg⁻¹). Sodium chloride (0.17 mol/l) infusions were given to another group of control animals. Each treatment was given to eight animals and results were compared by Student’s t-test.

Results

Table 1 shows the changes in mean arterial pressure and splanchnic nerve activity in the second hour of infusion. Only propranolol affected either significantly, causing a fall in arterial pressure and a parallel fall in splanchnic nerve activity. Practolol caused a lesser fall in arterial pressure and an increase in splanchnic nerve activity but these changes did not reach statistical significance.

Discussion

These results indicate that at least part of the hypotensive action of propranolol in the conscious rabbit is mediated by a centrally induced diminution in sympathetic nervous activity. The observation that practolol, in a greater β-adrenoceptor-antagonist dose, did not lower the arterial pressure, and did not have a central effect, suggests that the central effect of propranolol played an important part in the overall cardiovascular effect of the drug.

Propranolol exerts a hypotensive effect when given intraventricularly to the conscious rabbit (Reid, Lewis, Myers & Dollery, 1974), and this is associated with a diminution in splanchnic nerve activity. Practolol is also active when given into the cerebral ventricle (Day & Roach, 1974), but its low lipid solubility ensures that the drug does not cross into the brain and exert a central effect when it is given peripherally.

Although practolol has no central sympatholytic effect in this preparation it is an effective anti-hypertensive in man, as are other β-receptor blockers with low lipid solubility. It has been reported that catecholamine excretion is diminished in patients taking practolol, indicating some reduction in sympathetic nervous activity (Esler & Nestel, 1973). This remains difficult to explain but it is possible that since peripherally acting β-receptor blockers diminish cardiac responses to exercise and stress, the net effect of this may be to diminish autonomic sensory input to the central nervous system and hence eventually reduce the output of the central sympathetic nervous system.

Acknowledgment

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References


Increase of total body potassium and decrease of exchangeable sodium after long-term treatment with a $\beta$-receptor-blocking agent (prindolol) in essential hypertension

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Summary

1. The effect of long-term treatment with prindolol on blood pressure, total body potassium ($K_t$), exchangeable sodium ($Na_e$) and plasma renin activity was investigated in twelve patients with essential hypertension.

2. Systolic and diastolic pressures were significantly reduced from 164/112 to 127/90 mmHg under basal conditions.

3. Before treatment $Na_e$ in patients with essential hypertension was significantly higher than in normotensive individuals. After an average of 16 weeks on prindolol $Na_e$ in patients with essential hypertension was significantly decreased, despite an average increase in body weight of 2 kg in the patients.

4. In contrast to the decrease in $Na_e$, $K_t$ was found to be significantly increased after long-term treatment with prindolol. $K_t$ values of patients before and after prindolol, however, did not differ significantly from the corresponding sex- and age-dependent normal values.

5. Plasma renin activity was slightly diminished under basal and orthostatic conditions; the stimulatory effect of orthostasis was not abolished but reduced by prindolol.

6. It is suggested that the changes in sodium balance contribute to the anti-hypertensive effect of prindolol in patients with essential hypertension.

Key words: chronic effect of prindolol, essential hypertension, exchangeable sodium, plasma renin activity, total body potassium.

Introduction

Three main mechanisms contribute to the maintenance of arterial blood pressure: the sympathetic nervous system, the renin-angiotensin system and sodium balance. These mechanisms are closely interrelated. Their pathophysiological role in primary and secondary arterial hypertension has been the subject of many investigations. $\beta$-Receptor-blocking agents have been shown effectively to reduce blood pressure in patients with arterial hypertension (for review see Simpson, 1974). The mode of action by which $\beta$-receptor blockers reduce blood pressure has been attributed partially to a cardio depressive effect (Lydtin, Kusus, Daniel, Schierl, Ackenheil, Kempter, Lohmüller, Niklas & Walter, 1972), to an inhibitory effect on renin release (Büllner, Laragh, Baer, Vaughan & Brunner, 1972), to a reduction in sympathetic nervous activity (Lewis & Haeusler, 1975; Brecht, Banthien, Ernst & Schoeppe, 1976) and to a reduction of plasma volume (Tarazi, Fröhlich & Dustan, 1971). To date, none of these changes could exclusively explain the reduction in peripheral resistance which occurred after long-term treatment with $\beta$-receptor-blocking agents (Tarazi & Dustan, 1972). As the sodium-potassium balance plays a crucial role in arterial hypertension, we investigated whether the $\beta$-receptor-blocking agent prindolol interfered with sodium-potassium balance and whether the anti-hypertensive effect was related to changes in this system.

Methods

Patients

Twelve non-pretreated patients (two females,
ten males, 21–55 years old) with mild to moderate essential hypertension were studied. After a placebo period of 2 weeks, the patients were treated with 60 mmol (15 mg) of prindolol/day. The dose was raised individually every 2 weeks until blood pressure reached normal values (less than 145/100 mmHg after 5 min in a sitting position). The mean maximum daily dose was 170 mmol (35 mg) (range 60–360 mmol). When blood pressure because normal we reduced the dose to a daily mean maintenance dose of 114 mmol (28 mg) (range 60–360 mmol). The experimental treatment period on prindolol lasted between 9 and 27 weeks (average 16 weeks). During the study no other drugs (i.e. diuretics, contraceptives) besides prindolol were allowed, and no restriction was placed on the patients' diet with respect to salt and caloric intake. At the end of the placebo period and at the end of the experimental treatment period, total body potassium (K\textsubscript{t}), exchangeable sodium (Na\textsubscript{e}) and plasma renin activity were measured in all twelve patients.

K\textsubscript{t} and Na\textsubscript{e} were measured by means of a whole-body radioactivity counter (International Atomic Energy Agency, Directory of Whole-Body Radioactivity Monitors, IAEA, Wien 1970 Gy 2.1).

Measurement of K\textsubscript{t}

After phantom calibration of the counter the natural body radioactivity of \(^{40}\)K was determined by gamma-ray spectroscopy (energy band 1.33–1.59 MeV). The reproducibility was within ±5%. Accuracy of the values was confirmed by an intercomparison of phantoms and five persons with sixteen other European whole-body radioactivity counters (Smeets & Schmier, 1969). Normal values of K\textsubscript{t} and K\textsubscript{t,\textsubscript{Na}} (K\textsubscript{t}, related to kg body weight) were obtained on a group of 424 healthy individuals (347 males, seventy-seven females). Variations of K\textsubscript{t} and K\textsubscript{t,\textsubscript{Na}} with regard to age and sex were in agreement with the data of Oberhausen (1963) on more than 15 000 persons. K\textsubscript{t} in our patients was measured twice on 2 consecutive days.

Measurement of Na\textsubscript{e}

1 µCi of \(^{22}\)Na (\(^{22}\)NaCl) dissolved in 10 ml of sodium chloride solution (150 mmol/l) was injected intravenously. 15 min later and after an equilibration time of 48 h, whole-body radioactivity in the \(^{22}\)Na photo-peak region (energy band 1.15–1.41 MeV) was counted in the fasting patient after micturition. Immediately thereafter a venous blood sample was drawn, centrifuged and divided into two aliquots: one for the flame-photometric determination of plasma sodium concentration, the other for analysing \(^{22}\)Na radioactivity in a well-type scintillation counter against a standard of the injection solution. Na\textsubscript{e} was calculated by the formula:

\[
Na_e = \frac{m_t \cdot Z_e \cdot Z_{st} \cdot c_{Na,p}}{Z_e \cdot m_{st} \cdot Z_o}
\]

\(m_t = \) mass of \(^{22}\)Na solution injected;
\(m_{st} = \) mass of \(^{22}\)Na injection solution in the standard;
\(c_{Na,p} = \) concentration of sodium in the plasma sample;
\(Z_e = \) count rate of whole-body radioactivity counting 15 min after injection;
\(Z_{st} = \) count rate of whole-body counting after time of equilibration (48 h);
\(Z_o = \) radioactivity count rate of plasma sample in the well-type scintillation counter;
\(Z_{st} = \) radioactivity count rate of standard in the well-type scintillation counter (same volume and geometry as \(Z_o\)).

Normal values for Na\textsubscript{e} and Na\textsubscript{t,\textsubscript{Na}} (Na\textsubscript{e} related to kg body weight) were obtained from twelve healthy normotensive volunteer subjects (ten males, two females; 20–49 years of age): normal mean values of Na\textsubscript{e} and Na\textsubscript{t,\textsubscript{Na}} were 2870 mmol (sd 200) and 37.6 mmol/kg (sd 3.6).

Plasma renin activity (expressed as pmol of angiotensin I generated h\textsuperscript{-1} ml\textsuperscript{-1} of plasma) was measured by radioimmunoassay with a commercially available kit (NEN Chemicals GmbH, West Germany). To the incubation mixture (pH 5.5, 1 h) exogenous sheep substrate (Haas, Goldblatt, Gipson & Lewis, 1966) and Dowex resin were added.

For statistical analysis we used the non-parametric test of Wilcoxon for pair differences and the unpaired Student's t-test. The correlation coefficient and the test for existence of correlation were calculated by standard methods. \(P\) values represent the two-tailed error probability.

Results

Blood pressure and body weight

After an average of 16 weeks on prindolol systolic and diastolic pressure (measured after
Receptor blockade and exchangeable sodium

4 h in a supine position) were significantly reduced from an average value of 164/112 mmHg to 127/90 mmHg ($P < 0.001$).

Body weight increased considerably in all patients on prindolol by an average of 2.0 kg (range 0.3–4.1 kg) ($P < 0.005$).

Plasma renin activity

According to the renin values before prindolol treatment two patients could be classified as low-renin, one patient as high-renin and nine patients as normal-renin essential hypertensive, when plasma renin activity was related to the individual ratio of mmol of Na/g of creatinine in a single urine specimen (Goldberg & Spierto, 1973). On prindolol mean plasma renin activity was significantly reduced under basal conditions (4 h supine) from 2.41 (SD 1.40) to 1.93 pmol h$^{-1}$ ml$^{-1}$ (SD 1.00), $P < 0.05$. It should be noted that the two patients with low values even showed increased basal values on prindolol and one patient's plasma renin activity, which scored at the lower normal limit, did not change. After 2 h of walking, plasma renin activity in patients on prindolol was also significantly reduced, from 4.90 (SD 2.76) to 3.41 pmol h$^{-1}$ ml$^{-1}$ (SD 1.94), $P < 0.05$. Prindolol did not abolish the stimulatory effect of orthostasis: the percentage increase, however, was lower.

Sodium and potassium status (Fig. 1)

The mean $Na_e$ before prindolol was 3152 mmol (SD 600) and 41.6 mmol/kg (SD 2.25) respectively. Because of the large individual differences of body weight (52–105 kg) in our patients $Na_{e,s}$ is a better factor to compare with normal values. Mean $Na_{e,s}$ in patients before prindolol treatment was found to be significantly higher than in normotensive healthy individuals ($P < 0.005$). Mean $K_i$ in patients before prindolol was 3394 mmol (SD 420) and 45.4 mmol/kg (SD 5.92) respectively. When the individual values of $K_{i,s}$ were compared with corresponding age- and sex-dependent normal values (see the Methods section), no statistically significant difference could be found. After an average of 16 weeks on prindolol mean values for $Na_e$ and $Na_{e,s}$ were significantly reduced to 2915 mmol (SD 400) and 37.8 mmol/kg (SD 3.15) respectively, and $Na_{e,s}$ was no longer significantly different from the values derived from normal individuals. In contrast to the decrease of $Na_e$ and $Na_{e,s}$ respectively, $K_i$ was significantly increased to mean values of 3598 mmol (SD 429) and 46.9 mmol/kg (SD 5.68) respectively.

Fig. 1. Effect of long-term treatment with prindolol on exchangeable sodium ($Na_e$) and $Na_e$ related to body weight ($Na_{e,s}$) and total body potassium ($K_i$) and $K_i$ related to body weight ($K_{i,s}$) in twelve patients with essential hypertension.
Mean \( K\text{ss} \) in patients on prindolol was only slightly higher \((P<0.05)\) than before prindolol and did not differ significantly from the mean value of the corresponding sex- and age-dependent normal individuals.

The anti-hypertensive effect of prindolol was not related to the decrease in plasma renin activity, nor to the decrease in \( Na\text{s} \), nor to an increase in \( K\text{ss} \), because no significant correlations were found between the fall in blood pressure and the changes of these measurements.

**Discussion**

The most striking finding of the present study was a significant decrease of \( Na\text{s} \) and \( Na\text{ss} \), despite a concomitant increase in body weight after long-term treatment with prindolol. The mode of action by which \( Na\text{s} \) is diminished is not explained, and in particular we cannot conclude whether the reduction of \( Na\text{s} \) is the cause or the consequence of the fall in blood pressure. Both the sympathetic nervous system as well as the renin–angiotensin system are affected by chronic prindolol treatment, and as the sodium–potassium balance is closely interrelated with these two systems, changes in sodium balance may be due to changes in this complex system. Even though we could not detect a direct relation between the fall in blood pressure and the decrease in \( Na\text{s} \), a diminished \( Na\text{s} \) may certainly contribute to the blood pressure-lowering effect of prindolol in patients with essential hypertension.

**References**


