Effects of β-adrenoreceptor antagonists on sino-aortic baroreflex sensitivity and blood pressure in hypertensive man

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Summary

1. Sensitivity of the sino-aortic baroreflex was investigated before and after acute (23 patients) and chronic (23 patients) β-adrenoreceptor antagonism in patients with essential hypertension.

2. Sensitivity was inversely related to age ($r = -0.60$) and systolic blood pressure ($r = -0.46$); a positive relationship was noted between sensitivity and initial pulse intervals ($r = 0.40$).

3. Sensitivity increased significantly in patients less than 40 years of age after chronic treatment. No change occurred after acute treatment or in older patients treated chronically.

4. The fall in ambulatory intra-arterial blood pressure after chronic treatment was unrelated to alteration of baroreflex sensitivity.

Key words: β-adrenoreceptor, baroreflex, blood pressure, hypertension.

Introduction

β-Adrenoreceptor antagonists may lower blood pressure in man by altering sino-aortic baroreflex activity (Prichard & Gillam, 1969). However, the effects of these drugs on the baroreflex are controversial: acute intravenous administration causes a significant increase in baroreflex sensitivity in young subjects with normal blood pressure or borderline hypertension (Pickering, Gribbin, Strange Petersen, Cunningham & Sleight, 1972; Takeshita, Tanka & Nakamura, 1978). Chronic administration causes only minor or inconsistent changes in hypertensive patients (Hansson, 1973; Simon, Kiowski & Julius, 1977). The relationship between changes in blood pressure and baroreflex activity remains unclear. This study was undertaken to determine the effects of acute and chronic oral administration of β-adrenoreceptor antagonists on baroreflex sensitivity in hypertensive subjects and to examine the relationship between these effects and the hypotensive action of these drugs.

Patients and methods

Patients

Twenty-five patients (19 male, six female) with essential hypertension were studied. Mean age was $41 \pm 2$ years (mean $\pm$ SEM, range 17–54 years) and mean outpatient blood pressure was $172 \pm 4/107 \pm 2$ mmHg (range 145/95–200/122). We excluded subjects with secondary hypertension or with evidence of target organ damage (ischaemic heart disease or cerebrovascular disease, left ventricular hypertrophy, elevated serum creatinine or retinal changes greater than grade II). No patients had received hypotensive drugs within 2 months of study. Baroreflex measurements and bicycle exercise were performed on 21 patients on three occasions: first, before treatment; secondly, 3 h after the first oral dose of β-adrenoreceptor antagonist and finally after chronic treatment.
(mean duration 15 weeks, range 8–52 weeks). When studied after chronic treatment the last dose of treatment was taken at 08.00 hours on the day of admission and baroreflex testing was performed between 3 and 4 h later. In two patients observations were made before and after acute administration only. The following drugs were used for treatment: acebutolol 400 mg, propranolol 240 mg and metoprolol 200 mg, all administered once daily. Ambulatory intra-arterial blood pressure was recorded before and after chronic treatment in 22 patients. The patients were studied in hospital during two periods of 36–48 h duration. Sodium intake was standardized by asking patients to avoid adding salt to the diet apart from that used in cooking for 3 days before admission, and whilst in hospital they received 60 mmol of sodium daily.

Sino-aortic baroreflex activity

The method of Smyth, Sleight & Pickering (1969) was used. Measurements were made with the subject lying supine in a quiet room 40 min after bicycle exercise. On each occasion, an average of 4-6 (range 3–7) doses of phenylephrine (100 µg/ml; 0.49 mmol/l) were injected intravenously at intervals of at least 3 min sufficient to raise systolic blood pressure 15–30 mmHg. Blood pressure was measured from a polyethylene cannula (1 mm internal diameter) connected to a Gaeltec 3EA/a transducer and was recorded with electrocardiogram and respiratory movement on a Mingograf 81 recorder (Elema Schonander) at 50 mm/s. Systolic pressure of beats occurring from just before the rise in pressure to the maximum pressure was measured; beats occurring during inspiration were excluded. The pulse interval of the immediately following beat (phase 0) and the succeeding beat (phase 1) was measured (Pickering & Davies, 1973). Pulse interval (phases 0 and 1) was regressed on systolic blood pressure and the relationship with the highest correlation coefficient was selected; correlations with a probability of less than 0-05 were rejected. The regression coefficient (slope) measures baroreflex sensitivity (ms/mmHg). This method examines only the baroreflex response to increase in pressure and we did not study the effects of decreasing pressure on the baroreflex arc.

Ambulatory blood pressure measurement

Ambulatory blood pressure was recorded from the brachial artery cannula on a portable analogue tape recorder (Oxford Instruments) before and after chronic treatment (Littler, Honour, Sleight & Stott, 1972). Blood pressure was recorded as the average of ten observations measured from the paper playout during quiet afternoon activity.

Bicycle exercise

Upright bicycle exercise was performed for 8 min at a constant workload, determined from a previous maximal exercise test as the load causing 85% of maximum heart rate. Heart rate and blood pressure were recorded every minute during exercise on the Mingograph 81 recorder at 10 mm/s. Heart rate was averaged over 15 s and blood pressure averaged by digitizing 30 beats. The mean heart rate and systolic blood pressure during the last 3 min of exercise were used for analysis.

The investigations were approved by the Hospital Ethics Committee and informed consent was obtained from all patients.

Statistics

Results were expressed as mean ± 1 SEM. The significance of differences between means was tested by using Student's t-test for paired samples (two-tailed). Because of differences in variance before and after treatment (Snedecor's F-test), we used the U-test of Mann–Whitney to test the significance of differences in baroreflex sensitivity and reduction of exercise tachycardia on treatment (Siegel, 1956). Linear regression was calculated by the least-squares method with a Compucorp 344 calculator.

Results

Effects on blood pressure (Table 1)

Mean ambulatory blood pressure fell significantly after chronic treatment from 143 ± 4/80 ± 3 to 124 ± 4/66 ± 2 mmHg (P < 0.001).

Effects during exercise (Table 1)

Mean workload was 115 ± 9 W. β-Adreno-receptor antagonism was demonstrated by significant falls of exercise heart rate and systolic blood pressure after acute and chronic drug administration.

Baroreflex sensitivity before treatment

Sensitivity was inversely related to age (r = −0.60, P < 0.01) and decreased with increasing
Baroreflex and β-adrenoreceptor antagonists

Table 1. Effects of β-adrenoreceptor antagonists administered acutely and chronically.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Exercise heart rate (beats/min)</th>
<th>Baroreflex slope (ms/mmHg)</th>
<th>Average afternoon systolic blood pressure (mmHg)</th>
<th>Afternoon diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control acute</td>
<td>149 ± 5</td>
<td>106 ± 4</td>
<td>13.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>210 ± 3</td>
<td>189 ± 5</td>
<td>23.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Control chronic</td>
<td>149 ± 5</td>
<td>106 ± 4</td>
<td>23.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>210 ± 3</td>
<td>189 ± 5</td>
<td>23.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Mean baroreflex slope (sensitivity: ms/mmHg) before and after acute β-adrenoreceptor blockade. The line at 45° is the line of identity. ●, Acebutolol 400 mg; ■, metoprolol 200 mg; ▲, propranolol 240 mg.

Blood pressure, the relationship between baroreflex sensitivity and average afternoon systolic blood pressure ($r = -0.46, P < 0.05$) being stronger than that with mean pressure and diastolic pressure ($r = -0.42$ and $-0.34$ respectively). Initial pulse interval was averaged from the last three beats after phenylephrine injection before the pressure rose; baroreflex sensitivity was related to the initial pulse interval ($r = 0.40, P < 0.05$). The distribution of baroreflex slopes in this hypertensive population was non-Gaussian with a marked shift to the left; after logarithmic transformation, an approximately normal distribution was obtained.

**Baroreflex sensitivity after treatment**

Fig. 1 shows mean baroreflex slope before and after acute β-adrenoreceptor antagonism. The points are distributed evenly on either side of the line of identity and mean slopes, after logarithmic transformation, were 7.13 and 7.66 ms/mmHg respectively ($Z = 0.43, P > 0.1$).

After chronic treatment (Fig. 2) there was a tendency for points to lie above the line of identity and the mean slope was 7.39 ms/mmHg before treatment and 10.39 ms/mmHg after treatment, the increase being significant ($Z = 2.86, P < 0.05$).

An inverse relationship was observed between change in mean baroreflex slope after chronic treatment and age (Fig. 3, $r = -0.62, P < 0.01$). The increase in slope after chronic treatment was highly significant in the nine patients aged less than 40 years ($Z = 4.07, P < 0.001$) but was not significant in those aged more than 40 years ($Z = 0.83, P > 0.1$).
R. D. S. Watson, T. J. Stallard and W. A. Littler

FIG. 2. Mean baroreflex slope (sensitivity: ms/mmHg) before and after chronic β-adrenoreceptor blockade. Line of identity and symbols are as in Fig. 1.

FIG. 3. Change of mean baroreflex slope (sensitivity: ms/mmHg) after chronic β-adrenoreceptor blockade plotted against age (years). Symbols are as in Fig. 1.

After chronic treatment many patients showed a fall in blood pressure without a change in baroreflex sensitivity (Fig. 4). Neither the absolute nor percentage falls in systolic blood pressure were related to changes of baroreflex sensitivity ($r = 0.06$ and $0.14$ respectively). Percentage falls in systolic blood pressure in older and younger subjects were similar ($14 \pm 4\%$ fall in those aged less than 40 years; $12 \pm 2\%$ fall in those aged more than 40 years). When percentage change in systolic blood pressure was compared in patients who had changes in baroreflex slope more than or less than the median change, the values were similar (for systolic blood pressure: $12 \pm 3\%$ fall in those above the median and $14 \pm 3\%$ below; for diastolic blood pressure: $15 \pm 4\%$ fall for those above the median and $18 \pm 4\%$ fall in those below).

In patients studied on three occasions, initial pulse interval was significantly greater after chronic than after acute treatment (acute: $932 \pm 40$ ms; chronic: $1051 \pm 35$ ms; $P < 0.001$). In patients aged less than 40 years there was a linear relationship between the change in initial pulse interval and the change in baroreflex sensitivity after chronic treatment ($r = 0.71, P < 0.05$).

Differences between drugs

Chronic propranolol treatment caused a significant increase in baroreflex sensitivity (Table 2); because more patients (four of six) in this group were aged less than 40 years, this could have been due to differences between patients rather than between drugs. Chronic metoprolol treatment caused a significantly greater inhibition of exercise tachycardia than acebutolol treatment ($P = 0.02$) (Table 3); other differences were not significant.

Discussion

Our observations indicate that chronic β-adrenoceptor antagonism caused a significant increase in baroreflex sensitivity in hypertensive subjects aged less than 40 years, which was not seen after acute treatment. The observations of others are only partly in agreement with our observations and we need to consider the reasons for differences. Pickering et al. (1972) noted that acute intravenous administration of propranolol facilitated...
Baroreflex and β-adrenoceptor antagonists

TABLE 3. Effects of acute and chronic treatment on percentage inhibition of exercise heart rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute treatment</th>
<th>No. of patients</th>
<th>Chronic treatment</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>26 ± 2</td>
<td>11</td>
<td>23 ± 2</td>
<td>9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>24 ± 2</td>
<td>7</td>
<td>31 ± 2</td>
<td>8*</td>
</tr>
<tr>
<td>Propranolol</td>
<td>32 ± 5</td>
<td>3</td>
<td>31 ± 5</td>
<td>6</td>
</tr>
</tbody>
</table>

* Difference significant compared with acebutolol: \( P = 0.02 \) (Mann-Whitney \( U \)-test).

baroreflex sensitivity in young normal subjects; Takeshita et al. (1978) noted a similar effect in young patients with borderline hypertension whose mean age was 19 years. In contrast, Simon et al. (1977) were unable to demonstrate any effect of either intravenous propranolol or chronic oral timolol administration in hypertensive patients of mean age 40 years. An important difference relates to the initial heart rate: the subjects in the studies of Pickering et al. (1972) and Takeshita et al. (1978) had initial average heart rates of over 70 beats/min, similar to our patients; however, the hypertensive patients of Simon et al. (1977) had an average resting heart rate of only 59 beats/min. Pickering et al. (1972) showed that baroreflex sensitivity is inversely related to initial pulse interval and our results indicate that in hypertensive patients aged less than 40 years the response to β-adrenoceptor antagonism is related to the slowing of the initial heart rate. These observations point to a critical balance between parasympathetic and sympathetic tone at the sino-atrial node in determining baroreflex sensitivity and the response to β-adrenoceptor blockade. Kircheim (1976) has emphasized that controversy concerning the effects of β-adrenoceptor blockade on the response to carotid occlusion in the dog can be resolved by consideration of the effects of anaesthesia on the intrinsic heart rate: β-adrenoceptor antagonism abolished the response in anaesthetized animals with high sympathetic activity, but not in conscious animals with high vagal tone. Levy & Zieske (1969) have demonstrated, also in the dog, that the balance between sympathetic and parasympathetic activity is not simply additive and that a reduction in sympathetic frequency, which can be considered equivalent to β-adrenoceptor antagonism, causes less bradycardia in the presence of high background vagal tone than when vagal tone is low.

Consideration of the importance of age in determining the response to β-adrenoceptor an-
agonists clarifies further the disparities between our observations and those of others. The effects of age and high blood pressure in impairing baroreflex activity are well described (Griffin, Pickering, Sleight & Peto, 1971) and confirmed in our patients. We selected patients without target organ damage in order to minimize the effects of arterial wall thickening and cardiac hypertrophy on the reflex response. However, the observations of Takeshita et al. (1978) indicate that by the age of 20 years mild elevation of arterial pressure is sufficient to impair the baroreflex response. It is reasonable to suppose that as impairment of baroreflex activity progresses with sustained elevation of arterial pressure, it becomes increasingly difficult to show an effect of drugs on baroreflex sensitivity, as noted by Sleight & West (1974) with clonidine. Viewed in this light, our failure to demonstrate a significant effect of acute β-adrenoreceptor antagonism on baroreflex sensitivity becomes a relative rather than an absolute difference; in patients less than 40 years, there was a tendency for baroreflex slope to increase \((P = 0.2)\), which would have been more marked except for one patient who showed a decrease in slope. It is perhaps worth noting that the changes in baroreflex sensitivity after acute treatment were not significant in the six normal subjects described by Takeshita et al. (1978).

In summary, we consider that the level of background vagal tone and the degree of impairment of the baroreflex due to age and arterial hypertension are important factors which determine the response of the baroreflex to β-adrenoreceptor antagonism.

The observations of Angell-James & Bobik (1978) may further explain the differences between acute and chronic treatment observed in our patients. In renal hypertensive rabbits, continuous treatment with propranolol from the onset of hypertension had greater effects in increasing baroreflex activity towards normal than administration for only 2 weeks after hypertension had been present for several months. It is possible, therefore, that in young patients with relatively little arterial wall thickening, prolonged lowering of blood pressure by a mechanism independent of the baroreflex may allow repair of the deleterious effects of hypertension on the arterial wall with a consequent return of baroreflex activity towards normal. A similar effect was observed by Weiss, Lundgren & Folkow (1974), who found greater resolution of the structural vascular changes after treatment of young spontaneously hypertensive rats with β-adrenoreceptor antagonists than when older rats were treated.

We excluded inspiratory blood pressure beats from the measurement of baroreflex slope, as originally described by Smyth et al. (1969). Subsequently, Pickering et al. (1972) have included inspiratory beats in the analysis; although the correlation coefficient is influenced little by this procedure, the regression coefficient or baroreflex slope is significantly reduced (Pickering, 1970). We considered that exclusion of inspiratory beats was preferable because it could reduce variation in sensitivity due to sinus arrhythmia. A further difference in our analysis is that we used individual values of baroreflex sensitivity rather than comparing average values before and after treatment.

Finally, these observations need to be considered in relation to the hypothesis that alteration of baroreflex activity may have a primary role in the hypotensive effects of β-adrenoreceptor antagonists (Prichard & Gillam, 1969; Hansson, 1973; Takeshita et al., 1978). The evidence in favour of this hypothesis is based on the observation that a further fall in blood pressure occurred when chronic treatment was continued for some weeks after the titration of propranolol dosage to an optimum (Prichard & Gillam, 1969). It was suggested that resetting of the baroreceptors occurred so that pressor responses were buffered at lower pressures. Although a useful buffering effect may occur in younger patients, our observations do not provide evidence in favour of this being a primary effect of β-adrenoreceptor antagonists since baroreflex facilitation was observed only in patients less than 40 years of age and was independent of the hypotensive response to the drugs.

Although there are relatively more younger patients in the propranolol group, we do not think that our numbers are large enough to draw any firm conclusions as to whether a non-selective β-adrenoreceptor blocker behaves differently from a selective one. Indeed, we have found that once daily administration of β-adrenoreceptor antagonists reduced blood pressure substantially during sleep and physical activity throughout 24 h irrespective of whether or not they possess cardioselectivity, and our unpublished observations with the three drugs used in this study in exactly the same doses have not shown any significance between them. Arterial pressure was reduced throughout 24 h. Furthermore, exercise heart rate and exercise diastolic pressure were significantly reduced with
all the three drugs, as compared with control, 24 h after the last dose of treatment.

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References


