Br. J. clin. Pharmac. (1980), **10**, 133S–135S

HAEMODYNAMICS IN HYPERTENSIVE PATIENTS BEFORE AND DURING GUANFACINE TREATMENT

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1 The haemodynamic mechanisms underlying the antihypertensive effect of guanfacine during chronic oral administration were studied.

2 Ten patients with essential hypertension were submitted to haemodynamic measurements at rest and during exercise, before and after 12 weeks' treatment with guanfacine alone at a daily dose of between 3 and 15 mg orally.

3 The relevant haemodynamic values were obtained by means of an arterial catheter in the aorta, a venous catheter in the right atrium, and the measurement of cardiac output using the thermodilution method.

4 The antihypertensive efficacy of guanfacine was confirmed.

5 In the seven patients with a high peripheral resistance the main effect of guanfacine was a marked decrease in total peripheral resistance. In three patients with hypertension characterized by high stroke volume and cardiac output, the main effect of guanfacine was to reduce these variables.

Introduction

THE aim of the present study was to elucidate the haemodynamic mechanisms underlying the antihypertensive effect of guanfacine during chronic oral administration.

Methods

Patients

Ten patients with essential hypertension (WHO stage I to III) were submitted to haemodynamic measurements before and after chronic guanfacine administration. These patients were six men aged 27–55 yr (mean 42) and four women aged 41–59 yr (mean 49.3). Most of them had been newly diagnosed and had received no antihypertensive treatment before; and in those who were on treatment the antihypertensive drugs had been discontinued 2 weeks before the beginning of the trial. Informed consent was obtained from all patients.

Haemodynamic investigations

All patients were submitted to a haemodynamic investigation before guanfacine treatment was begun and to a second such investigation after 12 weeks' treatment period. The following variables were assessed at rest (supine) 5 and 15 min before effort, during exercise on the bicycle ergometer (25, 50, 75 and 100W, each for 2min), and 5 and 10min after exercise:

(1) systolic, diastolic and mean blood pressures in the aorta (arterial catheter via brachial artery);

(2) systolic, diastolic and mean blood pressures in the right atrium (venous microcatheter with Statham pressure transducer);

(3) heart rate; and

(4) cardiac output (thermodilution method).

From the above data the following values were calculated:

(1) Stroke volume and stroke volume index;

(2) cardiac index; and

(3) total peripheral resistance and resistance index.

The ECG (standard leads) was also recorded.

Guanfacine dosage

The patients received daily oral doses of guanfacine between 3 and 15 mg as the sole antihypertensive therapy for 12 weeks (mean 7.3 mg).

Results

Figure 1 shows the mean changes in all variables studied for the whole group. Before guanfacine treatment was begun, resting aortic blood pressure values, that is, the last values measured before the effort on the ergometer, ranged from 160 to 220 mg Hg systolic (mean 194) and from 80 to 116 mg Hg diastolic (mean 97). After the 12-week period of guanfacine treatment they ranged from 130 to 180 mm Hg systolic (mean 158) and from 55 to

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0306–5251/80/130133–03 $01.00

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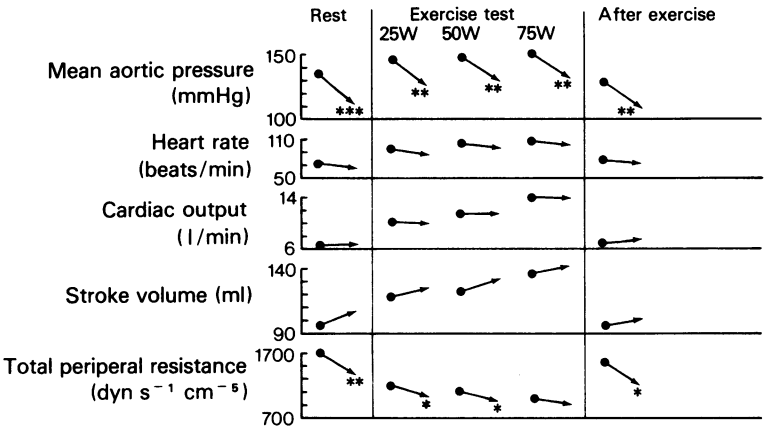

Figure 1 Haemodynamic parameters at rest, during exercise and after exercise, before (●) and after (▲) 12 weeks treatment with guanfacine.
*P < 0.05; **P < 0.01; ***P < 0.001.

95 mm Hg diastolic (mean 77). The reduction in resting systolic aortic blood pressure ranged from 19 to 60 mm Hg (mean 36) and that in the diastolic values from 10 to 43 mm Hg (mean 20). Resting heart rate fell from 71 to 65 beats/min on average during treatment, but the individual responses varied: a decrease was seen in six patients, an increase in three, and one remained unchanged.

At the highest performance level attained during exercise, aortic blood pressure before treatment ranged from 180 to 266 mm Hg systolic (mean 225) and from 75 to 124 mm Hg diastolic (mean 105). After treatment the values were 163 to 228 mm Hg systolic (mean 200) and 76 to 108 mmHg diastolic (mean 89). Maximum heart rate during exercise fell from 114 to 103 beats/min on average, increasing slightly in only one patient.

Resting cardiac output ranged from 4.93 to 9.13 l/min (mean 6.6) before treatment and from 4.96 to 8.47 l/min (mean 6.8) after treatment. Initial values of 7.7 l/min above decreased during treatment, whereas initial values between 7.07 and 5.52 l/min increased and low initial values (4.98 and 4.93 l/min) remained practically unchanged. The largest decrease in resting cardiac output was seen in a 26-yr-old man: from 9.13 to 6.47 l/minute.

Cardiac output during maximum physical performance ranged from 9.07 to 20.28 l/min (mean 14) before treatment and from 8.55 to 17.73 l/min (mean 13.5) after treatment. As a rule, higher initial values (13.27 to 20.28 l/min) decreased, whereas lower values (9.53 to 11.62 l/min) increased; but in one patient there was an increase from 14.70 to 15.91 l/minute.

Stroke volume at rest ranged from 60.6 to 146.6 ml (mean 97) before treatment and from 82 to 170.4 ml (mean 107) after treatment. It increased during treatment in seven patients (by 3.1 to 54.6 ml, mean 25.1) and was reduced (by 40, 28.5 and 2.5 ml, mean 23.7) in three patients with high initial values. (These patients also initially had remarkably high cardiac output and low peripheral resistance.)

Stroke volume at the maximum physical exercise level ranged from 67.5 to 235.8 ml (mean 127) before treatment and from 97.1 to 193.2 ml (mean 133) after guanfacine treatment. It increased during treatment in the same seven patients in whom it increased at rest (by 5.9 to 36.4 ml, mean 20.9) and decreased in the same three patients in whom it decreased at rest (by 42.6, 26.0 and 18.3 ml, mean 29 ml).

Resting total peripheral resistance before treatment ranged from 1038 to 2344 dyn s^{-1} cm^{-5} (mean 1631) and after treatment from 932 to 1824 dyn s^{-1} cm^{-5} (mean 1301). An increase was seen in only one patient (from 1038 to 1265 dyn s^{-1} cm^{-5}), in whom cardiac output had fallen from 9.13 to 6.47 l/minute. Resistance fell in all other patients, the greatest drop being by 786 dyn s^{-1} cm^{-5} (mean 392).

Total peripheral resistance during maximum physical exercise ranged from 426 to 1386 dyn s^{-1} cm^{-5} (mean 921) before treatment and from 466 to 1042 dyn s^{-1} cm^{-5} (mean 781) after treatment. A reduction was seen in seven patients (by 80 to 413 dyn s^{-1} cm^{-5}, mean 233) and an increase (by 40, 68 and 120 dyn s^{-1} cm^{-5}, mean 76) in three patients with low initial resistance values and high initial cardiac output.

Discussion and Conclusions

As can be seen from the above results, there is no single haemodynamic pattern accounting for the antihypertensive activity of guanfacine. Most of the patients studied had hypertension due to high

peripheral resistance, and the main effect in them was a lowering of peripheral resistance, while cardiac output remained practically unchanged or even increased in some instances. In the patients with high output hypertension, stroke volume and cardiac output were lowered, and peripheral resistance was clearly increased in one instance. There was no consistent pattern of influence on heart rate. Most haemodynamic changes were observable at rest and during exercise. However it should be noted that as this was an open study, at least part of the fall in blood pressure, cardiac output and heart rate could be attributed to the subjects becoming more familiar with the test situation.

In a similar investigation by Lund-Johansen (1974) in hypertensive patients treated with clonidine as the sole antihypertensive drug, it was shown that clonidine mainly reduced cardiac output and heart rate. These effects, though marked at rest, were negligible during maximum effort. Also, the effects of clonidine on peripheral resistance showed no consistent pattern and were judged disappointing. No differentiation, however, was made between various haemodynamic stages or forms of hypertension.

In the light of the available data, it is possible that the haemodynamic mechanisms underlying the antihypertensive activity of guanfacine are different from those that apply to clonidine. It is particularly interesting that, depending on the haemodynamic situation present, guanfacine proves effective in lowering the peripheral resistance.

Reference

LUND-JOHANSEN, P. (1974). Hemodynamic changes at rest and during exercise in long-term clonidine therapy of essential hypertension. *Acta med. Scand.*, **195**, 111–115.