Br. J. clin. Pharmac. (1977), **4**, 469–474

THE EFFECT OF MENTAL ARITHMETIC IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS, AND ITS MODIFICATION BY β-ADRENERGIC RECEPTOR BLOCKADE

G. NYBERG*, R.M. GRAHAM & G.S. STOKES
Cardiovascular Clinic and Cardiorenal Unit, Sydney Hospital, Sydney N.S.W. 2000, Australia

1 The effects of a 5-min period of sustained mental arithmetic upon blood pressure and heart rate were determined in several groups of healthy subjects and hypertensive patients.

2 The arithmetic produced significant increases in heart rate and blood pressure (both systolic and diastolic) in both normotensive and hypertensive subjects.

3 The blood pressure changes were neither attenuated nor enhanced by the prior administration of β-adrenergic receptor blocking drugs (alprenolol, propranolol or metoprolol) on an acute or chronic basis.

4 In subjects habituated to the test the heart rate increase was unaffected by the drugs, but in those less familiar with the test it was usually attenuated.

5 Although the β_1-adrenoceptor selective blocker, metoprolol, caused decreases in baseline values for blood pressure and heart rate similar to those observed with the use of the two non-selective blockers, it was shown in a double-blind crossover comparison with propranolol that the haemodynamic changes provoked by the mental arithmetic were not less in the presence of β_1-receptor blockade than when both β_1- and β_2-receptors were blocked.

6 These findings suggest that, during β_2-adrenoceptor blockade, the haemodynamic effects of minor mental stress are not exaggerated because of uncompensated α-receptor mediated vasoconstriction, such as occurs following adrenaline infusion.

Introduction

In subjects treated with the β_1- and β_2-adrenoceptor blocking agent, propranolol, infusion of adrenaline increases diastolic blood pressure. This effect is not seen during β_1-receptor blockade with practolol (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968) or metoprolol (Åblad, Carlsson, Dahlöf & Ek, 1975; Johnsson, 1975a and b), and appears to result from blockade of the peripheral β_2 vasodilator action of adrenaline, with unmasking of its α-receptor mediated vasoconstrictive effect. Thus, the β_2-adrenoceptor blocking propensity of propranolol and similar agents with β_1 and β_2 receptor affinity used in controlling hypertension could be deleterious during situations in which endogenous adrenaline release is increased.

Mental stress tests have been shown to cause increases in heart rate and mean blood pressure (Brod, Fencl, Hejl & Tirka, 1959), and increased urinary excretion of adrenaline and noradrenaline (Nestel, 1969). However, it is not clear whether the catecholamine release, neural or adrenal, occurring with this type of stress affects vascular β_2-adrenoceptors in the same way as infused adrenaline.

The following studies were performed to determine the pattern of cardiovascular responses to mental arithmetic and to assess the influence of various β-adrenoceptor blocking drugs upon this pattern.

Methods

Blood pressure was taken by the indirect cuff method with the subject seated. A standard protocol was used (Table 1), always with the same investigator. Recordings were done with minimal delay between the different sections of the protocol, and took 15–20 min depending on the blood pressure levels.

* Present address: Medical Department I, Sahlgrenska Hospital S-413 45 Göteborg, Sweden

Table 1 Protocol for tests of isometric exercise and mental arithmetic

Approximate time (min)	
0	Patient seated
1–5	Three successive blood pressure readings
6	First isometric test
7	Post-exercise reading
8	Second isometric test
9	Post-exercise reading
10–16	Mental arithmetic + Five blood pressure readings
17	Post-exercise reading

Resting values reported are means of the five resting recordings prior to mental arithmetic.
Results from the isometric tests will be published elsewhere.

Heart rate and blood pressure measurements were taken with an Auto Manometer® (Electronic Research and Development, Dunedin, New Zealand). This device was described in a previous paper (Nyberg, 1977).

Mental arithmetic was done by continuously substracting 17 from a four-digit number as quickly as possible, for 5 minutes. The subjects wrote down the answers on a standardized form ruled into columns, and were asked to start a new column each minute.

All studies were done in the morning following a light breakfast. Between the sessions, the hypertensive patients waited in the ordinary waiting room, and the normotensive volunteers performed normal clerical activities.

In all studies, Student's *t*-test has been used for statistical calculations, paired two-tailed from within-patient comparisons, and unpaired two-tailed for between-patient comparisons.

Pilot studies in normotensive and hypertensive subjects

Six healthy male subjects without history of cardiac or bronchial disease were studied before and 90 min after taking metoprolol (100 mg) orally.

Ten patients with established arterial hypertension, (mean age 45 years, range 23–66; seven were WHO grade I, two grade II, and one grade III (WHO, 1962)) had been treated with metoprolol 200–300 mg daily for at least a month, but had not taken the drug 24–36 h prior to the study. They were investigated using the protocol before and 90 min after metoprolol (100 mg).

Eight hypertensive patients had been treated with either alprenolol (200–400 mg twice daily, seven patients) or propranolol (one patient, 80 mg twice daily) for at least 3 months. Mean age was 50 years with a range of 36–57. Six were WHO grade I, one grade II and one grade III (WHO, 1962). They too had stopped their treatment 24–36 h prior to the study and were investigated before and 90 min after their normal morning dose (including diuretic where present).

Comparison of two dose-levels of metoprolol with placebo in healthy subjects

Six healthy males, age range 23–45 years (mean 33) took part. None of them had a previous history of hypertension, cardiac disease or bronchial disease. They gave their informed consent to participation in this study. After a training session, the subject performed the protocol twice on three different days, once before and once 90 min after intake of tablets of either placebo, 25 mg or 100 mg metoprolol tartrate. Tablets of 50 mg were used, together with identical placebo, and made up so that the doses were unknown to both subject and investigator. The different doses were given in randomized order in a Latin square design.

Figure 1 Protocol for double-blind crossover trial of metoprolol and propranolol

	Placebo	*Metoprolol/propranolol*						*Placebo*			*Propranolol/metoprolol*				
Weeks	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Clinic visits with blind blood pressures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Isometric exercise and mental arithmetic						x[1]	x			x					x
Metoprolol dose [2]	Nil	200/200–400 mg/day						Nil			160–329 mg/day				
Propranolol dose [2]		200–300 mg/day									160–240 mg/day				

[1] Training session
[2] Dose was increased at weeks 4, 6, 20 and 22 if standing diastolic pressure was 85 mm Hg and above, provided side effects did not preclude this course. Dose was not changed at weeks 8, 10, 24 and 26.

Double-blind crossover comparison of metoprolol and propranolol in patients with arterial hypertension

Seven patients (two females aged 37 and 49 years and five males aged 25, 28, 48, 52 and 53 years) previously untreated, and of WHO grade I (4) or II (3), entered a 28-week trial, the design of which is apparent from Figure 1.

At 10, 12, 18 and 28 weeks of the trial, the isometric exercise—mental arithmetic protocol as in Table 1 was performed between 09.00 h and 11.00 h in the morning. The patients came fasting except for their normal morning dose of trial drug treatment.

Results

Pilot studies

Figure 2 depicts the blood pressure and heart rate values at rest, during and immediately after administration of the drug in the three groups tested.

Before the drug, the stress produced significant increases in both systolic and diastolic blood pressure and in heart rate. The percent increases in blood pressure were very similar for all three groups (9–11% in systolic pressure and 9–13% in diastolic). The increase in heart rate was 21% for the normals and 15% for the hypertensive patients previously treated with metoprolol, but only 5% for the hypertensive who had received the other β-adrenoceptor blockers. However, the percentage falls in blood pressure and heart rate after cessation of the stress were similar between all groups (9–12%).

Ninety minutes after administration of the appropriate β-adrenoceptor blocker arithmetical stress produced changes in blood pressure which, although the baseline values were lower, did not differ significantly from those observed before the treatment. The rise in heart rate during the test and the fall after the test, was significantly attenuated by the metoprolol (by 50–67%, $P \leqslant 0.05$ or better) and slightly less influenced in the alprenolol-propranolol group (only heart rate fall after the test was attenuated by 50%, $P \leqslant 0.05$). The corresponding rises and falls in blood pressure were not affected by the drugs.

An analysis of the time-course of changes during mental arithmetic has been done by comparing the first and last values during the stress. In none of the groups was there any significant difference in either blood pressure or heart rate between these points. However, since the systolic pressure in normotensive and hypertensive *males* appears to be significantly higher at the first reading than the last (Nyberg, 1976), the two hypertensive groups were pooled and the sexes were analysed separately. It was then found that in the hypertensive males of the present study systolic pressure was also significantly higher (by 7 mm Hg, $P \leqslant 0.05$) at the first reading than the last during the stress *before drug*, but not during the stress *after drug*.

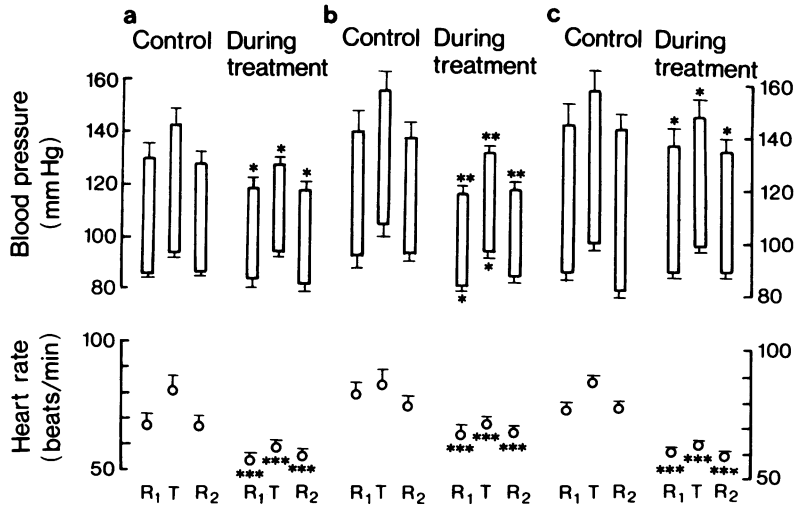

Figure 2 Blood pressure and heart rate (mean ± s.e. mean) at rest before (R_1), during arithmetical stress (T = mean of five readings) and 1 min after stress (R_2) in six normal male subjects (a) before and after treatment with metoprolol, (b) in eight hypertensive patients before and after alprenolol or propranolol and (c) in ten hypertensive patients before and after metoprolol. Asterisks indicate significance levels compared with the corresponding values before treatment. *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$.
All changes at T were statistically significant ($P \leqslant 0.05$ or $\leqslant 0.01$) by comparison to R_1 or R_2.

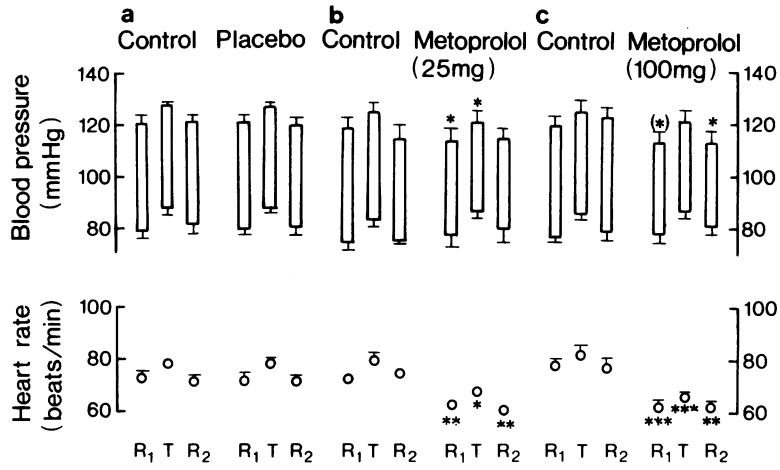

Figure 3 Blood pressure and heart rate (mean ± s.e. mean) at rest before (R_1), during arithmetical stress (T = mean of five readings) and 1 min after stress (R_2) in six normal male subjects before and after treatment with (a) placebo (b) metoprolol (25 mg) and (c) metoprolol (100 mg).
Asterisks indicate significant levels compared with the corresponding values before treatment. *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$.

For the five females whose blood pressure increased as much as the males, the same tendency was apparent although this was not statistically significant (5 mm Hg, $P \leqslant 0.10$).

Dose-response study in normals

Average values for blood pressure and heart rate before, during and after mental arithmetic, as well as the average rise and fall during and after the stress respectively, are given in Figure 3.

Resting values. No significant changes were seen after the placebo was given.

After metoprolol (25 mg), heart rate fell from 73 to 63 beats/min (13%, $P \leqslant 0.01$), and systolic pressure from 119 to 114 mm Hg (4%, $P \leqslant 0.05$).

After metoprolol (100 mg), heart rate fell from 78 to 62 beats/min (21%, $P \leqslant 0.01$) and systolic pressure from 120 to 113 mm Hg (6%, $P \leqslant 0.10$).

Heart rate and systolic blood pressure were significantly lower following metoprolol (25 mg) than following placebo ($P \leqslant 0.01$ and $P \leqslant 0.02$ respectively). Although there were no differences between the 25 mg and 100 mg dose with respect to post-tablet levels of heart rate and blood pressure, the change in heart rate from pre-tablet values was significantly greater on 100 mg than on 25 mg ($P \leqslant 0.02$).

Values during mental arithmetic. In all cases tested the stress-induced rises in blood pressure (systolic 4–8%, diastolic 10–12%) and heart rate (5–10%) before drug administration were similar to those after drug. However, the fall in systolic pressure after stress was greater following metoprolol (100 mg) (7%, $P \leqslant 0.05$) than after placebo or 25 mg.

Heart rate and systolic blood pressure levels during arithmetic were lower following 25 mg than following placebo (11 beats/min, $P \leqslant 0.05$ and 6 mm Hg, $P \leqslant 0.05$, respectively). Diastolic pressure level was unchanged. Following the 100 mg dose, values were similar to the 25 mg values.

Crossover study in hypertensive patients

Five patients undertook both periods on metoprolol (200 mg) daily and propranolol (160 mg) daily respectively. One patient needed metoprolol (300 mg) and propranolol (160 mg), and another metoprolol (200 mg) and propranolol (240 mg) for adequate control of standing diastolic blood pressure to be obtained (as specified in the protocol). The average daily doses were thus 214 mg for metoprolol and 171 mg for propranolol.

Figure 4 gives the values obtained at the end of the two drug periods as well as the placebo period. All values for blood pressure and heart rate were significantly lower ($P \leqslant 0.01$ or better) before, during and after mental arithmetic on metoprolol as compared with placebo. There was no significant difference between the two active drugs. The rises during arithmetic and fall after arithmetic were unaffected by both drugs with regard to blood pressure. The rise in heart rate during the test was, however, significantly attenuated by both drugs (by 50–75%, $P \leqslant 0.05$).

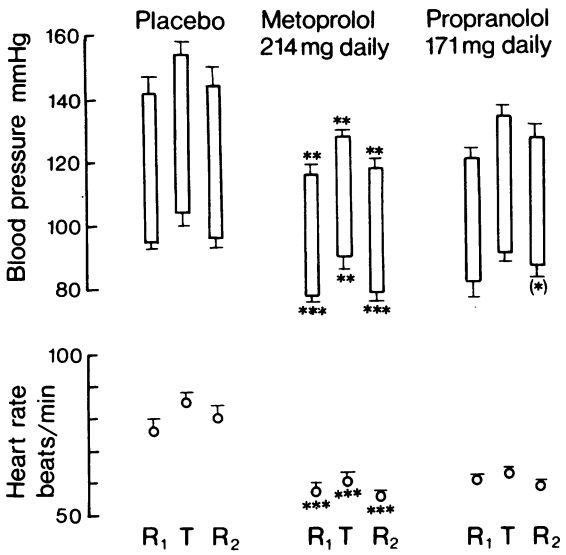

Figure 4 Blood pressure and heart rate (mean ± s.e. mean) at rest before (R_1), during arithmetical stress (T = mean of five readings) and 1 min after stress (R_2) in seven hypertenisve patients before and after treatment with (a) placebo (b) metoprolol (214 mg daily) and (c) propranolol (171 mg daily).
Asterisks indicate significance levels compared with the corresponding values before treatment. $^{*}P \leqslant 0.05$, $^{**}P \leqslant 0.01$, $^{***}P \leqslant 0.001$.

Discussion

The findings indicate that mental arithmetic stress causes prompt increases in heart rate and blood pressure (systolic and diastolic) in normotensive males and hypertensive subjects of both sexes. The onset of these effects occurred within 1 min of undertaking the stress, and they subsided within 1 min of stopping it. During the stress, blood pressure tended to fall slightly, in keeping with the findings of Ludbrook, Vincent & Walsh (1975), who measured blood pressure intra-arterially during mental arithmetic. Thus, in our normotensive and hypertensive male subjects there was a statistically significant decrease in systolic blood pressure from the first to the fifth measurement during the stress.

The decrease in resting blood pressure levels during the studies in hypertensive patients could to some extent be a consequence of the rest in the waiting room between tests. Six hypertensives who underwent the described protocol before and after receiving a placebo tablet had a mean fall in resting blood pressure of 6/5 mm Hg and a mean fall during mental arithmetic of 5/8 mm Hg without change in heart rate; statistical significance ($P \leqslant 0.05$) was achieved only for the resting diastolic pressure fall (Nyberg, unpublished observations).

The β-adrenergic receptor blocking drugs significantly attenuated the heart rate response to arithmetic in two of the three pilot study groups and in the cross-over trial of metoprolol and propranolol. They did not affect it in the dose-response study in normals, perhaps due to a familiarization with the test in subjects of the latter study.

The time-course of the blood pressure response to mental arithmetic and the failure of propranolol to affect this response suggest that it was not due to increased circulating adrenaline, which has been shown to raise diastolic blood pressure in the presence of β_1- and β_2-adrenoceptor blockade (Brick *et al.*, 1968; Johnsson, 1975a and b). Further, if the stress-induced pressor effect was due to sympathetic neural activity, the noradrenaline released at the neuro-effector junction clearly had little effect on vaso-dilatory β_2-receptors, for the rise in diastolic pressure was not exaggerated by agents with β_2-adrenoceptor blocking propensity (alprenolol, propranolol); these produced much the same effects as the β_1-adrenoceptor blocker, metoprolol. This is consistent with a relatively weak β_2-adrenoceptor agonist activity for noradrenaline, as shown by Lands, Arnold, McAuliff, Luduena & Brown (1967).

This issue has important practical implications in understanding the relevance of uncompensated α-adrenoceptor mediated vasoconstriction in hypertensive patients subjected to stress during β-adrenoceptor blockade. The present results clearly show that whether vascular β-adrenoceptors are blocked or unblocked, has little quantitative importance in situations of mild stress. The implications of this issue might be quite different in relation to strong emotional stimuli which recruit adrenaline secretion from the adrenal medulla. Here, diastolic pressure would be expected to rise more in the presence of β_1- and β_2-adrenoceptor blockade than when a selective β_1-adrenoceptor blocker like metoprolol is used, as in the adrenaline infusion experiments of Johnsson (1975a). However, it is difficult to study such strong stimuli under controlled conditions. Perhaps further information should be obtained by long-term intra-arterial or indirect blood pressure monitoring (Littler, Honour, Sleight & Stott, 1972; Sokolow Perloff & Cowan, 1973), during which cardiovascular reactions to incidental emotional trauma could be studied in relation to the different β-adrenoceptor blockers.

From the practical point of view, the present results are reassuring inasmuch as it is clear that the blood pressure level during light mental stress is not higher with treatment with adrenergic β-receptor blockers than without. West, Honour, Sleight & Littler (1976) have recently demonstrated, by using continuous intra-arterial blood pressure monitoring, that the

diurnal variations in blood pressure in hypertensive patients are not affected by β-adrenoceptor blocking drugs. They found that the effect of β-adrenoceptor blocker therapy was simply to lower the blood pressure level around which vacillations occurred. It may be important to compare β-adrenoceptor blockers with other anti-hypertensive agents in this respect, since the long-term organ effects of hypertension may well be related, not only to the average level of blood pressure but also to the rate of change of pressure within the vascular system, from beat to beat and from minute to minute (O'Rourke, 1976). Indeed, a general argument for using β-adrenoceptor blockers in hypertension is that they reduce heart rate and rate of rise to systolic pressure by their inhibition of inotropic β-adrenoceptors.

References

ÅBLAD, B., CARLSSON, E., DAHLÖF, C. & EK, L. (1975). Some aspects on the pharmacology of adrenergic β-receptor blockers. *Pathophysiology and management of arterial hypertension.* (Proceedings of conference in Copenhagen, eds G. Berglund, L.G. Hansson and L. Werkö. pp. 152–166).

BRICK, I., HUTCHISON, K.J., McDEVITT, D.G., RODDIE, I.C. & SHANKS, R.G. (1968). Comparison of the effects of ICI 50172 and propranolol on the cardiovascular responses to adrenaline, isoprenaline and exercise. *Br. J. Pharmac.*, **34**, 127–140.

BROD, J., FENCL, V., HEJL, Z. & JIRKA, J. (1959). Circulatory changes underlying blood pressure evaluation during acute emotional stress (mental arithmetic) in normotensive and hypertensive subjects. *Clin. Sci.*, **19**, 269–279.

JOHNSSON, G. (1975a). Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta pharmac. tox.*, **36**, 59–68.

JOHNSSON, G. (1975b). Selectivity studies with adrenergic β-receptor blockers in man. *Pathophysiology and management of arterial hypertension.* (Proceedings of conference in Copenhagen, eds G. Berglund, L.G. Hanson & L. Werkö. pp. 183–192.)

LANDS, A.M., ARNOLD, A., McAULIFF, J.P., LUDUENA, F.P. & BROWN Jr., T.G. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature, Lond.*, **214**, 597–598.

LITTLER, W.A., HONOUR, A.J., SLEIGHT, P. & STOTT, F.D. (1972). Continuous recording of direct arterial pressure and electrocardiogram in unrestricted man. *Br. med. J.*, **3**, 76–78.

LUDBROOK, J., VINCENT, A. & WALSH, J.A. (1975). Effects of mental arithmetic on arterial pressure and hand blood flow. *Clin. exp. Pharmac. Physiol.*, suppl. 2, 67–70.

NESTEL, P.J. (1969). Blood pressure and catecholamine excretion after mental stress in labile hypertension. *Lancet*, **i**, 692–694.

NYBERG, G. (1976). Blood pressure and heart rate response to isometric exercise and mental arithmetic in normotensive and hypertensive subjects. *Clin. Sci. mol. Med.*, **51**, suppl. 3, 681s–685s.

NYBERG, G. (1977). Indirect blood pressure and heart rate measured quickly without observer bias using a semi-automatic machine (Auto-manometer). Response to isometric exercise in normal healthy males and its modification by adrenergic β-receptor blockade. *Br. J. clin. Pharmac.*, **4**, 275–281.

O'ROURKE, M. (1976). Pulsatile aortic pressure flow relationships in hypertension. *Aust. N. Z. J. Med.*, **6**, suppl. 2, 40–48.

SOKOLOW, M., PERLOFF, D. & COWAN, R. (1973). The value of portably recorded blood pressures in the initiation of treatment of moderate hypertension. *Clin. Sci. mol. Med.*, **45**, 195s–198s.

WEST, M.J., HONOUR, A.J., SLEIGHT, P. & LITTLER, W.A. (1976). Blood pressure variability in patients on β-blockers. *Aust. New Z. J. Med.*, **6**, suppl. 3, 19–22.

WORLD HEALTH ORGANISATION (1962). Arterial hypertension and ischaemic heart disease. *Technical Report Series No. 231.*

(Received August 13, 1976)