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β-adrenoceptor antagonists increase sinus arrhythmia, a vagotonic effect

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1 The influence of vagal and sympathetic efferent activity on sinus arrhythmia in man has been studied in six healthy subjects by administration of hyoscine butylbromide and/or various β-adrenoceptor blocking drugs using a microcomputer-linked electrocardiogram system. Sinus arrhythmia was quantitated as the s.d. of the R-R interval.

2 Sinus arrhythmia was almost abolished by hyoscine butylbromide irrespective of the absence or presence and nature of the β-adrenoceptor blocking drug.

3 Atenolol and metoprolol alone prolonged the mean R-R interval and increased sinus arrhythmia. Oxprenolol, a drug with modest partial agonist or intrinsic sympathomimetic activity (ISA), prolonged the mean R-R interval to a lesser extent but had no effect on sinus arrhythmia. Xamoterol, which has high ISA, shortened the mean R-R interval but had no effect on sinus arrhythmia. These data yielded a non-linear relationship between sinus arrhythmia and mean R-R interval.

4 Exaggerated sinus arrhythmia appears to accompany β-adrenoceptor blockade only in the absence of ISA when bradycardia ensues. These findings are consistent with the hypothesis that the exaggeration in sinus arrhythmia is due to a central vagotonic effect secondary to the action of the drugs in the periphery.

5 Changes in R-R interval induced by the adrenoceptor blocking drugs were altered to some extent by vagal blockade. This observation is consistent with the hypothesis that changes in heart rate induced by such drugs are determined in part by a change in vagal tone.

Keywords sinus arrhythmia β-adrenoceptor blocker

Introduction

Sinus arrhythmia is a cyclical variation of heart rate with respiration maximal at a young age, which is thought to be mediated by fluctuation in vagal activity (Kunze, 1972). The evidence in favour of an exclusively vagal efferent pathway is that sinus arrhythmia is abolished in animals by vagotomy (Samaan, 1935; Anrep *et al.*, 1936; Hamlin *et al.*, 1966) and in both animals and man by cholinoceptor blockade (Hamlin *et al.*, 1966; Wheeler & Watkins, 1973).

Despite the existence of appropriately timed efferent activity in sympathetic nerves (Adrian *et al.*, 1932; Joels & Samueloff, 1956), propranolol is reported not to alter sinus arrhythmia in animals or man (Hamlin *et al.*, 1966; Wheeler & Watkins 1973; Katona & Jih, 1975). Recent work from

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this department (Coker *et al.*, 1984) has, however, demonstrated the conflicting finding that sinus arrhythmia in healthy human volunteers is enhanced by β-adrenoceptor blockade with atenolol. A possible explanation of the increase in sinus arrhythmia caused by atenolol is that it may have a central vagotonic effect (Coker *et al.*, 1984). If so, such an effect might determine, at least in part, the associated bradycardia and it could be anticipated that other β-adrenoceptor blocking drugs would increase the arrhythmia only insofar as they slow the heart rate.

The latter possibility has been investigated by measuring sinus arrhythmia in young healthy volunteers whose basal heart rates were altered by treatment with β-adrenoceptor blockers of differing partial agonist or intrinsic sympathomimetic activity (ISA). The drugs chosen were atenolol, metoprolol, oxprenolol and xamoterol. Atenolol and metoprolol lack ISA. By contrast, oxprenolol has modest activity and xamoterol, a newer β_1-selective adrenoceptor agent, possesses high ISA. In the dog the latter has been shown to possess 43% of the full agonist activity of isoprenaline on heart rate (Nuttall & Snow, 1982); in other animal species (Malta *et al.*, 1985) and in man (Hashimoto *et al.*, 1986) it has comparable effects.

Methods

Subjects

Experiments were performed on six healthy volunteers (two male, four female) aged 19–24 years. None had a history of asthma, cardiovascular disease or extrasystoles. One subject was taking a combined oral contraceptive, but no other medications were reported. The study received ethical approval from the Research (Endowments) Committee of the West Lambeth Health Authority and the subjects gave written consent to participate.

Procedure

The subjects attended on 5 experimental days separated by at least 1 week. On each occasion they fasted overnight except for an early morning non-caffeinated drink. The following drugs were taken single blind as conventional tablets with water 90 min before the experimental session:

atenolol	100 mg
oxprenolol	80 mg
xamoterol	200 mg

or dummy tablets only in a triple dummy experiment using a Latin square design. In the second phase (1 session) five of the subjects (the sixth was not available to take part) knowingly took:

metoprolol	100 mg

in order to verify that the changes already observed with atenolol were not unique to that drug.

The volunteers rested quietly in the supine position for the duration of the experiment. Measurements of heart rate, mean R-R interval and standard deviation of the interval (SDRR; as the measure of sinus arrhythmia) over successive 100 heart beat periods were obtained using an on-line microcomputer-linked ECG (Smith & Smith, 1981). Control measurements, continued until the resting heart rate was reached and in every case for a minimum of 20 min, were obtained from the last three such periods.

After control measurements, hyoscine butylbromide 0.4 mg kg^{-1} was administered as a single intravenous bolus and the ECG measurements continued until the heart rate returned to the control value. Values for mean R-R interval and SDRR obtained during periods of rapid heart rate change (i.e. immediately following the injection) were discarded. The investigation is based on all remaining values (26 to 50 per subject in each experiment). Blood pressure was measured by sphygmomanometry.

Statistical analysis

Drug effects on resting mean R-R interval, SDRR and mean blood pressure (before administration of hyoscine butylbromide) were assessed by analysis of variance using a nested classification (Snedecor & Cochran, 1967). This method allows for variable numbers of data points as in these experiments in which one subject did not receive one of the treatments. The statistical significance of differences between means were assessed by a multiple range test (Duncan, 1955). Repeatability of the measurements was derived from the residual mean square; the coefficients of variation were found to be: resting mean R-R interval 2.0%; SDRR 20.3%0; ratio SDRR/R-R interval 19.7%, in agreement with previous reports. Slopes of the linear relationship between mean R-R interval and SDRR for different β-adrenoceptor blocking drugs were compared by analysis of covariance using standard methods.

Results

Resting values

All the β-adrenoceptor blocking drugs altered mean R-R interval and therefore heart rate to a

significant extent (Table 1). By comparison with dummy treatment (957 ms HR 63 beats min^{-1}), atenolol, metoprolol and oxprenolol increased the interval to 1154 (52 beats min^{-1}), 1136 ms (53 beats min^{-1}) and 1040 ms (58 beats min^{-1}) respectively. Xamoterol shortened it to 894 ms (67 beats min^{-1}).

Sinus arrhythmia was exaggerated by atenolol and metoprolol, SDRR increasing from 66 to 174 ($P < 0.01$) and 139 ms ($P < 0.01$) respectively. Oxprenolol and xamoterol were without significant effect (Table 1) though they differed significantly from each other in this respect. Comparison of the five treatments revealed a non-linear positive relationship between mean R-R interval and SDRR (Figure 1). Only atenolol and metoprolol induced a significant increase in the ratio SDRR/mean R-R interval (Table 1).

Systolic blood pressure was significantly reduced by pretreatment with atenolol and metoprolol, unaffected by oxprenolol and increased by xamoterol (Table 1). Diastolic pressure was reduced by xamoterol but was unaffected by the other treatments (Table 1).

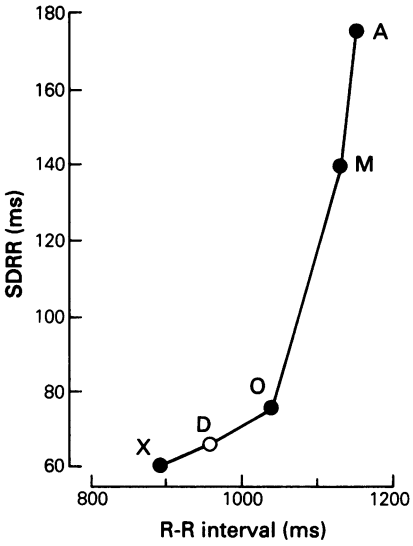

Figure 1 Effect of β-adrenoceptor blocking drugs on mean R-R interval and SDRR. A = atenolol; M = metoprolol; O = oxprenolol; D = dummy; X = xamoterol.

Cholinoceptor blockade

Cholinoceptor blockade with hyoscine butylbromide alone increased the heart rate, shortening the mean R-R interval by an average of 358 ms. This effect was exaggerated in the presence of β-adrenoceptor blocking drugs, atenolol to 445 ms (not significantly), metoprolol to 434 ms ($0.1 > P > 0.05$), oxprenolol to 449 ms ($P < 0.05$) and xamoterol to 406 ms (not significantly). Minimum values for R-R interval are given in Table 2.

The influences of the β-adrenoceptor blocking drugs on R-R interval were modified in the presence of hyoscine butylbromide (Figure 2). The effects of atenolol, metoprolol and oxprenolol (which increased R-R intervals) were

Table 1 Mean R-R interval, SDRR and ratio (×100) ± s.e. mean (between subjects) for different treatments

	Atenolol	*Metoprolol*	*Oxprenolol*	*Dummy*	*Xamoterol*	F *ratio Between drugs within subjects*
Mean R-R interval (ms)	1154 ± 60	1136 ± 72	1040 ± 49	957 ± 71	894 ± 52	115.8***
Δ R-R interval from dummy (ms)	198 ± 64	179 ± 43	83 ± 51		−62 ± 45	
SDRR (ms)	174 ± 42	139 ± 28	75 ± 13	66 ± 14	60 ± 8	29.6***
Ratio SDRR/Mean R-R (×100)	14.6 ± 3.3	11.6 ± 2.0	7.1 ± 1.1	7.0 ± 1.5	6.8 ± 0.9	20.7***
Systolic BP (mm Hg)	103 ± 2.5	102 ± 3.2	111 ± 4.8	111 ± 4.3	130 ± 4.2	167.6***
Diastolic BP (mm Hg)	62 ± 2.4	63 ± 2.5	67 ± 2.0	67 ± 1.2	62 ± 2.0	3.035*

* $P < 0.05$, *** $P < 0.001$

Treatments underlined indicate means which do not differ significantly from each other ($P > 0.05$)

Table 2 Effect of β-adrenoceptor blocking drugs on response (mean ± s.e. mean) of R-R interval and SDRR to hyoscine butylbromide (HBB)

	Atenolol	*Metoprolol*	*Oxprenolol*	*Dummy*	*Xamoterol*
Minimum R-R interval after HBB (ms)	710 ± 38*	701 ± 26**	591 ± 7	599 ± 28	488 ± 14**
Δ R-R interval from dummy (ms)	111 ± 21	102 ± 18	−7 ± 27		−110 ± 19
Minimum SDRR after HBB (ms)	5.6 ± 2.2	5.4 ± 0.8	4.0 ± 0.3	5.0 ± 0.7	2.4 ± 0.4*
Minimum ratio SDRR/Mean R-R (×100)	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.5 ± 0.1**
Slope SDRR/ RR interval	0.37***	0.31***	0.18	0.15	0.15

Differences from dummy treatments: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

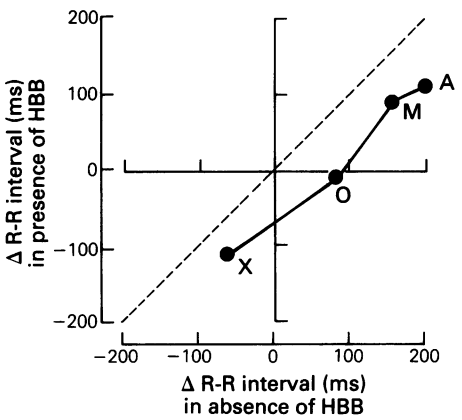

Figure 2 Effect of β-adrenoceptor blocking drugs on mean R-R interval in the absence and presence of hyoscine butylbromide (HBB). The interrupted line is the line of identity. A = atenolol; M = metoprolol; O = oxprenolol; X = xamoterol.

attenuated, that of xamoterol (which reduced R-R interval) was amplified. The overall difference from identity was highly significant ($P < 0.01$).

Sinus arrhythmia was almost abolished by hyoscine butylbromide under all conditions. Minimum values for SDRR ranged from 1 to 9 ms and were slightly lower under treatment with xamoterol (Table 2) than with the dummy tablets.

Within each individual a straight line relationship was found between SDRR and mean R-R interval (r values ranged from 0.670 to 0.920). The slope value obtained with hyoscine butylbromide alone (0.15 ms/ms) did not differ from those found after oxprenolol or xamoterol. Pretreatment with atenolol and metoprolol increased the slope of this relationship to 0.37 and 0.31 ms/ms respectively (Table 2).

Discussion

The observations made here have confirmed our previous findings that β-adrenoceptor blockade can increase sinus arrhythmia in man. The present results indicate that this occurs with metoprolol as well as with atenolol as was shown in an earlier study. Comparing the values obtained with various β-adrenoceptor blocking drugs of differing intrinsic sympathomimetic activity suggests that arrhythmia is enhanced only when the R-R interval is increased, i.e. when the heart rate is slowed. Contrariwise there is a trend towards a decrease in arrhythmia when R-R interval is shortened, i.e. when the heart rate rises, though the difference is not statistically significant. Thus a non-linear relationship is revealed between R-R interval and its variation. This suggests that under conditions of varying sympathetic tone heart rate and its variability are closely linked, presumably because they share a common cause.

Sinus arrhythmia is thought to be mediated exclusively through the vagus. The present experiments were consistent with this belief in that the arrhythmia was all but abolished by cholino-

ceptor blockade in every instance irrespective of the nature of the pretreatment. The suggestion was therefore made earlier (Coker *et al.*, 1984) that the increase in sinus arrhythmia provoked by atenolol is due to excitation of central vagal motor nuclei as a reciprocal accompaniment to reduction in central sympathetic outflow determined reflexly by the action of the drug in the periphery (Scott, 1983). The present results would appear to be consistent with such an hypothesis to the extent that metoprolol had the same effect as did atenolol. The two β-adrenoceptor blocking drugs with significant ISA did not accentuate sinus arrhythmia and it must be presumed that this is due to their differing effects on afferent reflex inputs, though a possible role of their differing influences on β_2-adrenoceptors cannot be excluded.

The nature of the afferent inputs remains to be elucidated. Blood pressure as such seems an unlikely determinant of the central vagal activity because, as argued before, the changes induced are in the wrong direction.

It has been suggested (Coker *et al.*, 1984) that, if the increased sinus arrhythmia associated with β-adrenoceptor blockade is produced by a central vagotonic influence, such an influence may also determine in part the accompanying bradycardia. Interpretation of the present findings in the light of this hypothesis is complicated by the major differences in R-R interval (and heart rate) induced by hyoscine butylbromide, the vagal blocking drug employed in these experiments. Nevertheless, in each case vagal blockade was found to attenuate to a small extent the change in R-R interval produced by the β-adrenoceptor blocking drug. The findings tend, therefore, to support the above hypothesis and indicate that changes in heart rate produced by β-adrenoceptor blocking drugs are in part due to alterations in vagal tone.

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