THE EFFECT OF INTRINSIC SYMPATHOMIMETIC ACTIVITY OF β -ADRENOCEPTOR BLOCKERS ON CIRCADIAN HEART RATE

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1 The effect of a β -adrenoceptor blocker without intrinsic sympathomimetic activity (propranolol) and a β -adrenoceptor blocker with ISA (pindolol) on circadian heart rate was studied in 10 patients (3 women and 7 men) with an average age of 55 years and the following diagnoses: coronary heart disease ($n=7$) and hypertension ($n=3$). The therapy was carried out in a randomized, cross-over study, with 3×40 mg propranolol and 3×5 mg pindolol.

2 Propranolol lowered the averaged circadian heart rate significantly ($P<0.001$) from 78 to 68 beats/min. The rate decreased both during the day and at night and the reduction was greater the higher the control value. The minimal hourly heart rate also decreased significantly ($P<0.005$) from 65 to 59 beats/min.

3 After pindolol the averaged circadian heart rate was not markedly changed. It reached a stable rate of around 70 beats/min. At a heart rate of below 70 beats/min an increase in rate was observed, whereas above 70 beats/min a reduction was found. The mean heart rate during the day remained unchanged. There was a significant relationship between the level of the control heart rate and the decrease in rate ($r=0.85$, $P<0.005$).

4 In a bicycle exercise test of 1 Watt/kg body weight over a period of 6 min, both β -adrenoceptor blockers lowered blood pressure and heart rate to the same extent.

Introduction

To what extent is the presence of intrinsic sympathomimetic activity important in the clinical use of a β -adrenoceptor blocker?

The aim of the study was to examine the influence on circadian heart rhythm as well as the effectiveness of β -adrenoceptor blockade by a drug without (propranolol) and one with intrinsic sympathomimetic activity (pindolol).

Methods

After informed consent was obtained an inpatient study was carried out in a total of three women and seven men with an average age of 54.9 years (range 41–66 years), with the following diagnoses, coronary heart disease ($n=7$) and hypertension ($n=3$).

On the first day (i.e. first day without medication which acted as a control) at 08.00 a commercially available Holter recorder (ICR) was applied and an electrocardiogram was made in 2 leads for 24 h without medication. At 11.00 h a bicycle exercise test was carried out with the patient in a sitting position and a work load of 1 Watt/kg body weight over a 6 min period. Before and after the test the patients' blood

pressure was measured according to Riva Rocci and the heart rate was determined by electrocardiographic tracing. At the end of the first 24 h without medication (08.00 h) the patients were treated in random order with 5 mg pindolol or 40 mg propranolol *per os*.

Three hours later (11.00 h) the exercise test was repeated. At 14.00 h and at 20.00 h another dose of 5 mg pindolol or 40 mg propranolol was administered.

The next day (08.00 h) there was again an exercise test (end of the treatment). After an interval of 72 h without therapy the procedure was repeated with alternating medication.

The well-known contraindications against β -adrenoceptor blockers were respected. During the test the patients did not receive any other therapy and special attention was paid to see that no tranquillizers or hypnotics were given.

The statistical comparisons were carried out with the *t*-test for paired differences. In addition, the sign patterns were analysed according to Dixon-Mood.

The regression analyses were based on the principle of the least squares; all the correlation coefficients are product–moment correlation coefficients.

Figure 1 Pattern of the heart rate over 24 h. ○○○○ pindolol, ●●●● control before pindolol, — propranolol, --- control before propranolol. * $P < 0.1$, ● $P < 0.05$, ●● $P < 0.01$, ●●● $P < 0.001$.

Results

Circadian heart rate

The circadian pattern of the heart rate is shown in Figure 1. The control values before pindolol (105,325 heart beats in 24 h) and propranolol (110,662 heart beats in 24 h) were, except for minor differences (at 17.00 h, 21.00 h and 22.00 h) comparable. Propranolol caused a significant ($P < 0.001$) reduction of the total number of heart beats to 97,102 in 24 h. Contrary to this, the number of heart beats after pindolol remained practically unchanged at 109,497. This means that after propranolol there was a significant decrease ($P < 0.001$) of the averaged circadian heart rate from 78 to 68 beats/min, whereas after pindolol no significant change was observed (Table 1).

Effect on the heart rate during the day and at night: (Table 1)

During the day (09.00 h to 20.00 h) the heart rate after propranolol decreased significantly ($P < 0.001$) from 82 to 72 beats/min and at night (23.00 h to 03.00 h) from 69 to 62 beats/min ($P < 0.01$). After pindolol, during the day the heart rate remained unchanged and at the night there was an increase ($P < 0.01$) from 65 to 75 beats/min. Correspondingly, the minimal heart rate after pindolol rose from 61 to 70 beats/min ($P < 0.005$), whereas propranolol caused a significant decrease ($P < 0.005$) from 65 to 59 beats/min. In all the patients taken together there was a total of 25 hourly segments after propranolol with average heart rates of less than 55 beats/min,

and in three cases the average hourly rate was even below 50 beats/min. With pindolol the average hourly heart rates were always over 55 beats/min.

Effect of medication on heart rate in relation to control value

Both during the day (Figure 2) and at the night (Figure 3) a significant relation was noted between the control value and the decrease in the heart rate after propranolol. After pindolol the heart rate pattern was different: in the case of a low control value it increased, in the case of a high control value it decreased. Yet, during the day from a rate of 71 beats/min upwards, the higher the control value ($r = 0.88$, $P < 0.01$), the greater the decrease in the rate.

Blood pressure and heart rate at rest and during exercise: (Table 2)

At rest the systolic and diastolic blood pressure was not significantly changed by either of the treatments. Propranolol reduced the heart rate at rest from 82 to 67 beats/min ($P < 0.01$).

This effect lasted for 24 h, but was not so marked at the final test period (heart rate 74 beats/min).

Pindolol also reduced the heart rate at rest. The reduction, however, was smaller than with propranolol and at the last examination after 24 h it was no longer detectable. During exercise both β -adrenoceptor blockers caused almost the same significant reduction in the increase of the systolic blood pressure. The effect on the heart rate was similar: there was no significant difference in the degree of

Table 1 Pattern of the heart cycles and heart rate over 24 h, as well as during the day and at night before and after propranolol and pindolol. (Mean $\pm$ s.d. results)

	QRS/24 h	QRS 09.00–20.00 h (Day)	QRS 23.00–03.00 h (Night)	Average heart rate in 24 h (beats/min)	Average heart rate 09.00–20.00 h (beats/min)	Average heart rate 23.00–03.00 h (beats/min)	Average heart rate (beats/min)
Control value propranolol	110.662 $\pm$ 14.572	58.678 $\pm$ 7.905	20.590 $\pm$ 2.744	77.4 $\pm$ 10.1	81.4 $\pm$ 11.1	68.6 $\pm$ 9.2	65 $\pm$ 8.3
Control value pindolol	105.325 $\pm$ 12.487	56.818 $\pm$ 6.409	19.478 $\pm$ 2.120	73.7 $\pm$ 8.8	79.6 $\pm$ 9.1	64.9 $\pm$ 7.1	61 $\pm$ 6.8
Propranolol	97.102 $\pm$ 10.377	51.212 $\pm$ 5.679	18.583 $\pm$ 2.229	68.0 $\pm$ 7.4	71.1 $\pm$ 7.9	61.9 $\pm$ 7.4	59 $\pm$ 7.0
Pindolol	109.497 $\pm$ 13.134	55.438 $\pm$ 5.816	22.320 $\pm$ 2.828	76.6 $\pm$ 8.3	77.0 $\pm$ 8.1	74.4 $\pm$ 9.4	70 $\pm$ 7.9
Control value propranolol v pindolol	$P < 0.05$	$P < 0.1$	$P < 0.1$	$P < 0.05$	NS	$P < 0.1$	$P < 0.1$
Control value propranolol v propranolol	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.01$
Control value pindolol v pindolol	$P < 0.1$	NS	$P < 0.01$	NS	NS	$P < 0.01$	$P < 0.01$
Control value propranolol v pindolol	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Figure 2 Heart rate between 09.00 h and 20.00 h before and after therapy with propranolol and pindolol. Linear regression lines before and after treatment with propranolol ($\bullet$, $y = 21.1 + 0.61x$, $r = 0.87$, $P < 0.01$) or pindolol ($\blacktriangle$, $y = 29.8 + 0.58x$, $r = 0.88$, $P < 0.01$), $n = 10$.

the reduction of the exercise-induced heart rate increase; thus we may assume an equally effective blockade of β -adrenoceptors within the period of observation, with the doses of the drugs used.

Discussion

As observed in other studies (Millar-Craig *et al.*, 1978), the maximal heart rates of our patients were recorded at about midday and thereafter there was a steady decline with the minimal circadian rate occurring at about 04.00 h. In the morning, there was an initial significant increase in heart rate, however, this remained below the level attained at midday. The fall in heart rate during the night has already been described by other authors (Lown *et al.*, 1973; Picker-

Figure 3 Heart rate between 11.00 h and 03.00 h before and after therapy with propranolol and pindolol. Linear regression lines before and after treatment with propranolol ($\bullet$, $y = 19.5 + 0.62x$, $r = 0.77$, $P < 0.01$) or pindolol ($\blacktriangle$, $y = 37.6 + 0.54x$, $r = 0.66$, $P < 0.05$), $n = 10$.

Table 2 Pattern of systolic, diastolic blood pressure and heart rate at rest and during exercise before (08.00 h) and after (11.00 h, 08.00 h) propranolol and pindolol. Mean $\pm$ s.d. results

		At rest			During exercise		
		08.00 h Control value	11.00 h	08.00 h	08.00 h Control value	11.00 h	08.00 h
Systolic BP (mm Hg)	Propranolol	153 $\pm$ 26	146 $\pm$ 26*	151 $\pm$ 26	185 $\pm$ 33	167* $\pm$ 21	173 $\pm$ 31
	Pindolol	147 $\pm$ 26	146 $\pm$ 20	148 $\pm$ 19	180 $\pm$ 31	168 $\pm$ 22	174 $\pm$ 27
Diastolic BP (mm Hg)	Propranolol	100 $\pm$ 17	99 $\pm$ 17	96 $\pm$ 12	97 $\pm$ 19	96 $\pm$ 15	95 $\pm$ 13
	Pindolol	98 $\pm$ 12	95 $\pm$ 12	96 $\pm$ 12	97 $\pm$ 15	97 $\pm$ 12	96 $\pm$ 9
Heart rate (beats/min)	Propranolol	82 $\pm$ 15	67 $\pm$ 8**	74 $\pm$ 17	115 $\pm$ 18	93*** $\pm$ 11	97** $\pm$ 14
	Pindolol	79 $\pm$ 13	71 $\pm$ 11***	77 $\pm$ 12	114 $\pm$ 19	96*** $\pm$ 14	105* $\pm$ 16

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

ing *et al.*, 1977) and is the result of a predominance of parasympathetic nervous activity during the night (Baust & Bohnert, 1966; Samaan, 1934).

Propranolol, the antagonist lacking intrinsic sympathomimetic activity, produced a reduction in heart rate which was evident in all the hourly segments of the recording. However, the effects of pindolol were dependent on the prevailing state of sympathetic tone. During the night, when sympathetic tone is low, heart rate was increased after pindolol treatment reflecting the intrinsic sympathomimetic activity of the drug. During the daytime, at heart rates of 71 beats/min, corresponding to normal resting sympathetic tone, pindolol exerted little or no effect on heart rate but at higher frequencies, corresponding to raised sympathetic tone, the β -adrenoceptor blockade produced by the drug was reflected by a reduction in heart rate.

The difference between the two drugs is most clearly illustrated by the results of the exercise tests. Despite the fact that, unlike propranolol, pindolol hardly influenced resting heart rate, it was equieffective with the latter drug in inhibiting the exercise-induced tachycardia and increases in systolic blood pressure.

The results reveal that with an antagonist such as propranolol, which lacks sympathomimetic activity, the β -adrenoceptor blockade is apparent not only during periods of increased sympathetic activity but also under resting conditions. In contrast, pindolol, because of its intrinsic sympathomimetic activity, produces little or no depression of resting function and its antagonist effects only become apparent during periods of increased sympathetic activity. This is illustrated not only by the exercise tests but also by the circadian heart rate recordings which reveal that

the drug significantly lowered heart rate only during the segments at 11.00 h, 15.00 h and 17.00 h where high hourly heart rates had been recorded in the control period.

Other authors have reported that the sympathomimetic effects of pindolol render it less likely to produce negative inotropic effects and in contrast to drugs lacking this property, pindolol produces little or no reduction in resting cardiac output (Gebhardt, 1970; Svendsen *et al.*, 1979). The sympathomimetic effects of the drug are not confined to the heart but are also mediated at the β -adrenoceptors of other organs and several investigators have suggested that this property may represent an added safety feature in patients with obstructive pulmonary disease, cardiac insufficiency, bradycardia or peripheral circulatory disturbances.

The results of this study indicate that, in clinical practice, intrinsic sympathomimetic activity can protect against undesirable bradycardia. After pindolol treatment none of the hourly segments was below 55 beats/min whereas after propranolol a total of 25 segments showed heart rates of below 55 beats/min and in three of these the hourly average was below 50 beats/min. Similar results have been reported by McNeil & Louis (1979) who found that bradycardia occurred in 17% of patients receiving metoprolol, 31% receiving atenolol but in only 3.5% of patients receiving pindolol. It can be concluded that a β -adrenoceptor antagonist with a relevant degree of intrinsic sympathomimetic activity such as pindolol effectively inhibits β -adrenoceptor mediated responses in conditions of increased sympathetic activity without causing unnecessary depression of resting function.

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