PINDOLOL PHARMACOKINETICS IN RELATION TO TIME COURSE OF INHIBITION OF EXERCISE TACHYCARDIA

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1 Pharmacokinetics of pindolol were studied in normal subjects given 5, 10 and 20 mg orally and 3 mg i.v. Plasma half time was 2.9 ± 0.3 (s.e. mean) h for both routes; peak drug levels occurred 1–2 h after ingestion and bioavailability was 53%. Plasma protein binding was 38% and was independent of plasma concentration; the drug was not concentrated in the red cell.

2 Work-heart rate regression lines were calculated from resting heart rate and three grades of 'steady-state' exercise standardized for the maximum work capacity (W_{max}) of each subject. The equation was characterized by slope and HR_{50} (calculated heart rate at $0.5 W_{max}$).

3 After giving 5 mg i.v. pindolol to produce maximum cardiac β -adrenoceptor blockade there were differences in inhibition of resting heart rate, slope, HR_{50} and maximum heart rate suggesting differences in sympathetic components. However, estimates of the degree of inhibition were closely similar for each variable when determined before and after atropinization indicating that the accuracy of estimation was independent of the level of vagal activity.

4 After oral pindolol peak inhibition of resting heart rate, slope and HR_{50} coincided with peak plasma concentration. Peak reduction of resting heart rate was greatest at the lowest dose, but inhibition of slope and HR_{50} were similar at all doses.

5 The different heart rate parameters recovered at different rates. After 24 h slope had returned to control, and the residual inhibition of HR_{50} reflected residual β -adrenoceptor blockade of resting heart rate, as demonstrated by a shift in isoprenaline-heart rate relationship.

6 Inhibition of HR_{50} and other exercise parameters were 20% less in the concentration range 5–20 ng/ml than peak inhibition obtained in the range 21–160 ng/ml. The higher potency of pindolol compared with propranolol can be accounted for by the difference in protein binding.

Introduction

Pindolol is the most potent β -adrenoceptor blocking agent in clinical use (Pritchard, McDevitt & Shanks, 1976), and possesses intrinsic sympathomimetic activity (ISA). Recently Gugler, Hoebel, Bodem & Dengler (1975) showed that after a single 10 mg oral dose maximum inhibition of exercise tachycardia occurred at about 2 h and had declined by about half 4 h later. They found a close relationship between degree of inhibition and plasma pindolol concentration. This had been found earlier by Hicks, Arbab, Turner & Hills (1972) who, however, used lower doses than Gugler *et al.* (1975) and below those used clinically. Subsequently Aellig (1976) observed more prolonged inhibition after 5 mg oral pindolol with some residual inhibition still present at 24 h. This is inconsistent with Gugler *et al.*'s (1975) finding of a close relationship between plasma concentration and inhibition particularly since Gugler, Herold & Dengler (1974) had shown that 24 h after taking 10 mg plasma pindolol was less than 1 ng/ml.

In view of these apparently contradictory findings we have extended the pharmacokinetic analysis of Gugler *et al.* (1975) and reinvestigated the effects of three doses of oral pindolol on the time course of the resting heart rate changes—exercise response.

There appears to be uncertainty of the heart rate parameters that provide the best yardstick for assessing the level of β -adrenoceptor blockade (see review by McDevitt, 1977) and of the best type of exercise protocol to be used. For example, most studies of the effects of β -adrenoceptor-blocking drugs on exercise have used only a single level of exercise. Gugler *et al.* (1975) and Aellig (1976) each assessed different parameters of the exercise response which may have contributed to the difference in findings. In the present investigation we have determined the time-course of effects of pindolol on all the parameters of the work-heart relationship, which was derived from the resting heart rate and three levels of standardized graded 'steady-state' exercise. Robinson, Epstein,

Beiser & Braunwald (1966) and others have shown that the proportion of vagal and sympathetic effects on heart rate vary with the severity of exercise. Carruthers, Shanks & McDevitt (1976) have suggested that the level of vagal activity influenced the estimation of cardiac sympathetic inhibition by β -adrenoceptor blocking drugs. We have investigated this by comparing the inhibition of the sympathetic effects by pindolol on resting and exercise heart rate parameters before and after atropinization.

Methods

Subjects and dosage

The study was performed on twenty healthy volunteers. Their mean age was 27 years (range 21–34) and their average weight was 74.7 kg (range 61–88 kg). No medication was taken for 3 weeks before or (apart from pindolol) during the 4-week study period. The effects of 5, 10 and 20 mg pindolol and a placebo tablet were studied in five subjects and three more subjects received two oral doses. The others received one or more of the intravenous or oral doses. Effects of one dose or placebo were examined on any given day, and 1–2 weeks allowed between studies.

Pindolol assay

Samples of forearm vein blood (10 ml) were taken through a 20 gauge 'butterfly' cannula at the following times: just before giving pindolol, hourly for 7 h, with another sample at 24 h. Plasma pindolol was measured by the fluorimetric method of Pacha (1969). Fluorescence was measured using an Aminco Bowman spectrofluorimeter (excitation 395 nm and emission 440 nm). The limit of sensitivity of the assay varied between 6 and 8 ng/ml. The percent of [14 C]-pindolol bound to human plasma protein was determined *in vitro* by equilibrium dialysis as described by Evans, Nies & Shand (1973). Binding to plasma protein was determined for plasma concentrations of 8, 31, 56, 130 and 260 ng/ml and was calculated as (plasma concentration–buffer concentration)/plasma concentration. Distribution between erythrocytes and plasma was determined, using the method of Cotham & Shand (1975), by adding [14 C]-pindolol to heparinized blood (2 ml) to give whole blood concentrations of 50, 100 and 150 ng/ml.

Pharmacokinetic analysis

The observed plasma pindolol concentration-time data for each subject following intravenous administration of pindolol were fitted to a biexponential equation

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C_p is the plasma pindolol concentrations at time t after administration, α and β are the first order rate constants for the fast and slow disposition processes, A and B are the ordinate intercepts. The pharmacokinetic parameters of a standard two compartment open model were obtained from graphic estimates of each exponential (Table 1). After intravenous administration the area under the time-concentration curve (AUC) was calculated from

$$AUC = A/\alpha + B/\beta \quad (2)$$

After oral administration AUC was calculated by the trapezoidal method and the area beyond the last sample added according to equation 3, where AUC_0^t is the area, C_t is the last sample measured and β is the slope of the semilog plot of plasma concentration against time.

$$AUC = AUC_0^t + C_t/\beta \quad (3)$$

The bioavailability of pindolol was estimated from the ratio of the 'dose-corrected' means of the areas under the curve for oral and intravenous administration.

Exercise protocol and measurements

The exercise was performed on an Elema-Schonander bicycle ergometer. Heart rate was obtained from the ECG using an Avionics Exerstress 3000 monitor. Four consecutive sets of 15 beats were averaged during the last minute of the resting and 'steady state' periods of exercise. Resting systolic blood pressure was measured by sphygmomanometer, with the Korotkoff sounds obtained by a microphone placed over the brachial artery.

Details of the exercise protocol have been described previously (Bailey, Anderson, Rozea, Bernstein, Nyberg & Korner, 1976). Initially a set of graded 'sprint' exercises were performed solely to determine the subject's maximum work capacity (W_{max}). The test consisted of a 2 min initial period with no load, and work was then increased by 100 kilopond metres (kpm) each minute until the subject's W_{max} was reached either due to fatigue or discomfort. If a particular workload was not completed the duration of this period was rounded to the nearest half-minute and W_{max} expressed to the nearest 50 kpm. W_{max} of each subject was used subsequently to standardize the rate of work performed in steady state exercise before and after pindolol administration. W_{max} ranged from 900–1600 kpm (mean 1300 kpm); maximum heart rates were 173.5 ± 17.4 (s.e. mean).

'Steady state' measurements began with the subject seated on the bicycle after 45 min rest or later if the resting heart rate had not returned to within 5 beats/min of the pre-'sprint' value. After the resting measurements 4 min bouts of exercise were performed successively at rates of 0.25, 0.5 and 0.75 of W_{max} . Ten min later the subject ingested either 5 mg, 10 mg

Figure 1 (a): Regression lines calculated from data of subject J.M. before (●) and after (□) ingesting 20 mg oral pindolol. Each line relates rate of work (standardized in terms of 'sprint' W_{max}) and heart rate obtained at rest ($R=0$ W_{max}) and during 4 min graded exercises at rates of 0.25, 0.50 and 0.75 of W_{max} . Control response (●—●); after pindolol (□—□). R, R' are resting values and HR_{50}, HR'_{50} , heart rate min^{-1} at 0.5 W_{max} estimated from regression lines before and after drug.

(b): Changes in heart rate from rest observed during single level of exercise before and after pindolol. R, R' are resting values and E, E' exercise values before and after pindolol. Evaluation of drug effects as explained in text.

or 20 mg of pindolol or a placebo tablet, which were assigned in random order. The 'steady state' exercise protocol was repeated 1, 3, 5, 7 and 24 h later.

In agreement with Bailey *et al.* (1976) we found that the heart rates at 'sprint' W_{max} rates were closely similar to those observed in the same subjects during 'steady state' exercise at a rate of 0.75 W_{max} . Under the latter conditions mean heart rates were 167.9 ± 11.8 beats/min, suggesting that this work level was close to each subject's maximum capacity for sustained work. Bailey *et al.* (1976) found no significant change in W_{max} after intravenous alprenolol and we have previously found no change in patients with angina after intravenous pindolol (Jennings, Bobik & Korner, 1977).

In three subjects isoprenaline/heart period dose-response curves were obtained before and at 1, 24 and 72 h after ingesting 10 mg pindolol. The curves were obtained by the method of Cleveland, Rangno & Shand (1972) using increasing doses of isoprenaline given by rapid intravenous infusion. Shifts in the dose-response curves were expressed in terms of the dose of isoprenaline required to produce an increase in heart rate of 25 beats/min.

Analysis of exercise-related heart rate response

A linear regression equation adequately described the relationship between heart rate and 'steady state' workload (standardized as a fraction of each subject's sprint W_{max}), using the resting heart rate at zero workload, and the rates at the three normalized workloads of 0.25, 0.5 and 0.75 W_{max} to derive the equation (Figure 1). After β -adrenoceptor blockade the heart rate at any workload is lower and this may be due to the effects of the drug on resting heart rate, slope, or on both (see Figure 1). Accordingly we have examined the effects of pindolol or placebo on (i) resting heart rate R ; (ii) regression slope b ; (iii) the parameter HR_{50} which is the estimated heart rate at 0.5 W_{max} ; HR_{50} is influenced by changes in both resting heart rate and slope. The inhibition due to beta blockade of all these parameters expressed as a percentage of the control response was calculated from the equations

$$(1 - R'/R) \times 100;$$

$$(1 - b'/b) \times 100$$

and

$$(1 - HR_{50}'/HR_{50}) \times 100$$

where the numerator in the second part of the expression in brackets is the parameter after blockade, and the denominator the control value before blockade. We also examined the effects of pindolol on the observed value HR_{75} , where vagal effects are low (Robinson *et al.*, 1966; Carruthers *et al.*, 1976). Most studies have employed only a single level of exercise. In some, the effects of beta blockade have been expressed as

$$(1 - E'/E) \times 100$$

where E' and E are the heart rates after block and under control conditions at the same level of exercise (Figure 1, right panel) (see review by McDevitt, 1977). In others, the inhibition of exercise tachycardia has been calculated as

$$(1 - y/x) \times 100,$$

where

$$y/x = (E' - R')/(E - R)$$

(Figure 1, right panel). The first measure is analogous to the effect on HR_{50} , the second to the effects on slope of the parameters used in this paper.

Exercise studies with atropine

In four subjects the inhibition produced by 5 mg i.v. pindolol was determined on 2 experimental days 1 week apart, allocated at random as follows. On the first day sprint W_{max} was determined. This was followed on one day by measurement of resting heart

Figure 2 Mean and s.e. mean of time-concentration curves obtained in four subjects following 3 mg i.v. bolus of pindolol at zero time.

rate and the usual three grades of 'steady-state' exercise after which the subject received 5 mg i.v. pindolol and the above protocol was repeated 30 min after injection. On the second day after another set of control observations the subject was given atropine (0.04 mg/kg i.v. in a dose to block reflex vagal effects on heart rate, Korner *et al.*, 1973, 1976) followed by another set of resting and exercise measurements; the protocol was repeated 30 min after injecting 5 mg i.v. pindolol. Two subjects were studied on another day after injection of the above doses of pindolol + atropine and then carried out another set of exercises after a further 5 mg pindolol and 0.02 mg/kg atropine i.v.

Results

Pharmacokinetics

After a bolus i.v. injection the time concentration curve was fitted by two exponentials (Figure 2). In 4 subjects the mean half life of the initial α phase was 0.14 ± 0.01 (s.e. mean) h and of the β phase of 2.9 ± 0.3 h. The mean volume of distribution of the central compartment (V_1) was 43 ± 3 (s.e. mean) l and the apparent total volume of distribution ($V_d\beta$) was 86 ± 12.1 l (see Table 1 for other parameters).

After ingesting 5, 10 and 20 mg pindolol peak $\pm$ s.e. mean plasma pindolol concentrations were 22.5 ± 2.7 , 44.6 ± 6.6 and 95.8 ± 0.0 ng/ml respectively and occurred between 1–2 h (Table 2). Mean $\pm$ s.e. mean plasma half life was 2.9 ± 0.3 h (range 1.8–4.6 h) and was similar for all three doses. After 24 h pindolol was not detectable in plasma. Mean dose-corrected AUC was 52.5 ng h mg $^{-1}$ after i.v. administration which

Table 1 Pharmacokinetic parameters following 3 mg pindolol i.v.

Subject	A (ng ml $^{-1}$)	B (ng ml $^{-1}$)	α (h $^{-1}$)	β (h $^{-1}$)	k_e (h $^{-1}$)	k_{12} (h $^{-1}$)	k_{21} (h $^{-1}$)	V_1 (l)	$V_d\beta$ (l)	AUC (ng h ml $^{-1}$)	AUC (ng h ml $^{-1}$)	$T_{1/2\beta}$ (h)
1	38.5	27	4.56	0.25	0.57	2.22	2.03	46	111	116	38.81	2.74
2	51	34.6	6.39	0.22	0.52	3.38	2.72	35	87	157	52.42	3.12
3	26.4	32.4	5.55	0.20	0.35	2.25	3.14	51	93	167	55.59	3.52
4	17.7	57.2	4.28	0.31	0.40	0.85	3.34	40	53	189	62.88	2.22
Mean	33.4	37.8	5.2	0.25	0.46	2.18	2.88	43	86	157	52.43	2.9
(s.e. mean)	(7.3)	(6.7)	(0.5)	(0.03)	(0.05)	(0.52)	(0.03)	(3.5)	(12)	(30)	(10.08)	(0.30)

V_1 = central volume of distribution; $V_d\beta$ = total volume of distribution; k_{12} , k_{21} = rate constants between central and peripheral compartments of standard model; k_e = elimination rate constant from central compartment; other symbols defined in equations (1)–(3).

Table 2 Pindolol plasma concentration (ng/ml) after oral doses of 5, 10 and 20 mg in five subjects

Time (h)	0.5	1	2	3	4	5	6	7	$AUC_{0-\infty}$ (ng h ml ⁻¹)	$AUC_{0-\infty}$ (ng h ml ⁻¹)	$T_{1/2}$ (h ⁻¹)
Pindolol 5 mg											
Mean plasma concentration (s.e. mean)	12.9 (5.7)	20.1 (4.3)	22.4 (2.7)	20.9 (2.0)	16.0 (1.5)	12.2 (1.4)	9.2 (1.0)	7.0 (1.1)	138 (14)	27.6 (2.8)	2.9 (0.2)
Pindolol 10 mg											
Mean plasma concentration (s.e. mean)	24.1 (5.2)	44.4 (6.6)	40.2 (2.5)	33.4 (3.1)	23.4 (2.6)	20.6 (3.4)	14.5 (2.8)	12.7 (2.5)	249 (39.2)	24.9 (3.9)	3.0 (0.5)
Pindolol 20 mg											
Mean plasma concentration (s.e. mean)	69.8 (22.4)	95.8 (25.1)	95.8 (11.8)	72.4 (5.2)	58.6 (4.4)	43.8 (5.2)	35.0 (3.6)	28.2 (3.0)	532 (40)	26.6 (2)	2.9 (0.4)

Figure 3 Relationship between mean areas under curve (AUC, ng h ml⁻¹) and dose of pindolol (mg) given orally ($n=5$ at each dose).

differed significantly from the value 27.6 ng h ml⁻¹ after oral pindolol (<0.05) (Tables 1 and 2). From these results mean bioavailability was estimated at 53%. AUC was linearly related to the oral dose and the extrapolated regression line passed close to the origin (Figure 3).

Pindolol binding to plasma proteins in four subjects estimated over the concentration range 8–260 ng/ml in each was relatively constant at $38 \pm 1\%$. The erythrocyte/plasma concentration ratios averaged 0.69 ± 0.04 and were constant at the different drug concentrations.

Heart rate responses after oral pindolol

Giving placebo tablets had no significant effects over the next 24 h on resting heart rate, slope and HR_{50} (Figure 4). After oral pindolol peak reduction in heart rate, slope and HR_{50} occurred 1–3 h after ingestion, at the time of peak plasma concentration (Figure 4). In this group where the effects of the different doses were not all studied in the same subjects there were no significant differences in peak inhibition of slope and HR_{50} between doses which averaged 26% and 22% respectively over the above parameters (Figure 4). Inhibition of resting heart rate was somewhat more marked at the lowest dose (26%) than at the other doses (14%, 19% respectively; $0.1 > P > 0.05$).

The time course of recovery was similar with the three doses and after 7 h resting heart rate had recovered only slightly, with an average 94% of peak inhibition still remaining. Recovery in resting

Figure 4 Time course of changes in resting heart rate (beats/min), slope (beats/min per unit standardized workload), HR₅₀ (beats/min) and resting systolic blood pressure, after 5, 10 and 20 mg oral pindolol or placebo. C=pre-pindolol control, other times are h after ingestion; data is mean and s.e. of mean from seven subjects except at 24 h where $n=4$; the seven subjects receiving each dose were not all the same.

heart rate was significantly less than in slope where 59% of peak inhibition still remained after 7 h (P for difference <0.025). Recovery in HR₅₀ was also smaller, with 79% of peak inhibition still remaining ($P<0.01$). Only four subjects reported for the test at 24 h and it was necessary to pool the results over all doses to assess the significance of the residual inhibition. At 24 h resting heart rate and HR₅₀ were respectively 12% and 31% of the peak inhibition and still significantly below control ($P<0.05$, 0.005 respectively) but slope had recovered (Figure 4). Over the entire time course changes in observed HR₇₅ closely paralleled the changes in HR₅₀. The regression of percentage inhibition calculated from HR₅₀ and that calculated from HR₇₅ was given by the equation

% Inhibition HR₅₀ = $-0.39 + 0.893\%$ Inhibition HR₇₅,
with a correlation coefficient of 0.931.

The maintenance of some beta adrenoceptor blockade at 24 h was confirmed in three subjects by

studying the effects of increasing bolus dose of isoprenaline at different times after pindolol. The dose-response curve (Figure 5) 1 h after 10 mg pindolol had become displaced to the right compared with the control curve so that on average 51 (range 22–100) times more isoprenaline was required to cause a similar increase in heart rate. After 24 h the average shift in the dose-response curve was still 10-fold (range 5.2–16.7) but after 72 h the curve was back to initial control. These subjects were studied in the supine posture and pindolol did not lower resting heart rate, which was 82 beats/min before and 83 beats/min after the drug, contrasting with the reduction in resting rate in the main study where the subjects sat on the bicycle ergometer (Figure 4).

Blood pressure response

Peak reduction in resting systolic blood pressure occurred between 1 and 3 h and averaged 6%, 18%

Figure 5 Isoprenaline dose-response curves from one subject before ($\square$) and 1 (Δ), 24 ($\bullet$) and 72 h ($\blacksquare$) after 10 mg oral pindolol.

and 8% of control with 5 mg, 10 mg and 20 mg respectively (Figure 4). Restoration of blood pressure was more rapid than of heart rate and after 5 h blood pressure did not differ significantly from control.

Dose-heart rate response relationship

The maximum inhibition of resting heart rate, slope and HR_{50} were estimated from five subjects who received every dose, by averaging the 1 and 3 h responses at each dose (Figure 6). Peak reduction in resting heart rate was greatest after 5 mg averaging 24.3% of control. This differed significantly from peak effects on resting heart rate of 14.8% and 17.9% obtained with 10 and 20 mg pindolol ($P < 0.025$). After 24 h this inverse relationship to dose was no longer observed and reduction of resting heart rate was now greater the greater the initial dose. Thus resting rates were reduced by 8%, 20% and 55% of the peak reduction 24 h after taking 5 mg, 10 mg and 20 mg respectively.

Peak inhibition of slope at 1–3 h was similar at each dose and averaged 25.6% of control over all doses. There was more individual variation with each dose of pindolol in the changes in this parameter. Peak inhibition of HR_{50} was relatively uniform and was similar at each dose (average 22% of control).

Plots from 6 individual subjects relating plasma pindolol concentrations to percent inhibition of HR_{50} (Figure 7) over the three oral doses at the different times of the study indicate that there was significantly more inhibition at plasma concentration above 20 ng/ml (average 21%) than below 20 ng/ml (average difference 17.2%, $P < 0.025$). There was little further increase in inhibitory effect in the range 21–160 ng/ml.

Figure 6 Relationship between peak reduction in resting heart rate, slope HR_{50} and resting systolic blood pressure (all expressed as % of control response) and peak plasma pindolol concentration (ng/ml) after taking 5, 10 and 20 mg pindolol. All results are means and s.e. means; n equals the same 5 subjects in each group.

Pindolol inhibition before and after atropine

Four subjects performed the standard exercise protocol under (i) control conditions; (ii) 30 min after 5 mg i.v. pindolol alone, when plasma concentration averaged 66 ng/ml; (iii) after atropine alone; (iv) after atropine + pindolol (Figure 8, Table 3). The relationship between heart rate and work remained linear with each type of autonomic block, but there were significant changes in intercept and slope (Figure 8, Table 3). Even after atropine + pindolol there was still a significant rise in heart rate with increased work. This was not due to inadequate block of the cardiac effectors since the same rise in heart rate occurred in two subjects after additional amounts of pindolol and atropine.

Figure 7 Results from six subjects showing relationship between plasma pindolol (ng/ml) and reduction in HR₅₀ (% of control) over the full range of the time-concentration curves.

There were no significant differences in the estimates of inhibition of resting heart rate, HR₅₀ or HR₇₅ produced by pindolol before and after giving atropine (Table 3, inhibition 1 and 2), nor were there any differences in the absolute reduction in heart rate under the two experimental conditions (cf. columns (a-b) and (d-e), Table 3). It should be noted that with either estimate there was an increasing degree of inhibition (expressed as % reduction of control rate) with rising workload within subjects ($P < 0.001$). This percentage inhibition was greater in HR₇₅ than in HR₅₀ which in turn had more inhibition than the resting rate. Taking the mean of the estimates of inhibition obtained before and after atropine the average inhibition was $16.0 \pm 2.54\%$ for resting heart rate, $22 \pm 1.02\%$ for HR₅₀ and $24.8 \pm 0.93\%$ for HR₇₅. The difference in the standard errors of the mean was significantly greater for resting heart rate than for the other two variables ($P < 0.05$). However, the standard errors of the difference of the two estimates of inhibition within-subjects were not significantly different for the above parameters, and were respectively 1.98, 1.59 and 1.72 (Table 3).

Vagal effects were estimated from the differences in absolute heart rate between columns (c-d). The mean vagal effect averaged -40.8 beats/min for resting heart rate, -16.6 beats/min for HR₅₀, and was only -6.3 (NS) at HR₇₅.

Estimates of slope before and after giving atropine were made by the formulae given in Table 3, and showed again reasonable agreement. The average sympathetic component of slope was 38% of the total autonomic response (range 28%–52% in different subjects).

The 16 pairs of comparisons of the estimates of inhibition before and after atropine (columns f, g, Table 3) had a correlation coefficient of 0.90, with a regression equation % Inhibition (atropine) = $5.75 + 1.19\%$ Inhibition (no atropine), where the standard error of the regression coefficient was 0.15

Figure 8 Regression lines showing relationship between heart rate/min and normalized work range (fraction of W_{max}) in subject KR studied on day 1 (a) under control conditions (C_1 , ●) and after 5 mg i.v. pindolol (P, ■), and on day 2 (b) under control conditions (C_2 , ●), after atropine (A, ○) and after atropine + pindolol (A + P, □). c shows the mean results obtained from all four subjects.

and the regression coefficient did not differ significantly from 1.

Discussion

Assessment of cardiac sympathetic inhibition

The present study has indicated that the different combinations of cardiac effector block all produce distinctive effects on slope and intercept of the regression of heart rate on work. In the experiments of Table 3 the dose of pindolol elevated plasma concentrations sufficiently to produce complete block of the cardiac sympathetic to reflex stimuli (Korner *et al.*, 1973, 1976). The estimates of inhibition made before and after atropine were in good agreement, indicating that the accuracy of estimating sympathetic block is not influenced by the differing contributions of the vagus to resting heart rate, HR₅₀ and HR₇₅.

The slope changes with the different combinations of autonomic block suggest that there is a progressive increase in sympathetic activity and simultaneously a progressive reduction in vagal activity from rest to the maximum 'steady-state' exercise studied. These results therefore do not support the earlier suggestion of Robinson *et al.* (1966) that the tachycardia of mild exercise is almost entirely due to reduction in vagal activity, followed by increasing sympathetic effects at

Table 3 Effects of different combinations of autonomic block

	Column						
	(a) Control 1	(b) Pindolol alone	(c) Control 2	(d) Atropine alone	(e) Atropine + pindolol	(f) Inhibition 1 ³	(g) Inhibition 2 ⁴
Heart rate (beats/min)	ML	110	107	145	132	12.7	9.0
	KR	85	90	125	107	17.6	14.4
	JR	83	86	126	94	20.5	25.4
	PC	66	60	110	95	15	13.6
	Mean ¹	86.0±9.1	85.8±9.7	126±7.2	107±8.8	16.5±1.7	15.6±3.5
	Δ ²	+14±1.5	-40.8±3.2	+19.5±4.3		0.9±1.98	
HR ₉₀ (beats/min)	ML	148.5	139	165.7	133.5	20.6	19.4
	KR	141.7	142.5	147.8	116.2	23.8	21.4
	JR	121.7	131.6	143.6	106.2	23.1	26.0
	PC	108.1	108.1	130.2	106.2	23.1	18.4
	Mean	130.0±9.3	130.3±7.7	146.8±7.3	115.5±6.4	22.7±0.7	21.3±1.69
	Δ	+29.4±1.9	-16.5±4.8	+31.3±2.8		1.4±1.59	
HR ₇₅ (beats/min)	ML	168	163	179	136	23.8	24.0
	KR	167	166	160	120	27.5	25.0
	JR	141	154	156	113	25.5	27.5
	PC	129	129	142	114	25.6	19.7
	Mean	151.3±9.7	153±8.4	159.3±7.6	120.8±5.3	25.6±0.8	24.1±1.63
	Δ	+38.8±2.8	-6.3±5.1	+38.5±3.6		1.5±1.72	
Slope	ML	78	74	45.6	6.0	45.1	58.2
	KR	107.6	98	48.4	17.6	36.8	38.3
	JR	75.6	92.8	42.8	25.6	30.1	25.5
	PC	85.6	86.8	43.6	25.6	38.3	29.4
	Mean	86.7±7.3	87.9±5.2	45.1±1.2	18.7±4.6	37.6±3.1	37.8±7.3
	Δ	32.6±3.6	42.8±5.0	26.4±5.4		0.3±4.8	

¹ Mean ± s.e. mean between subjects.² Δ ± s.d. within subjects.³ Inhibition 1 = (1 - b/a) × 100%.⁴ Inhibition 2 for resting HR, HR₉₀, HR₇₅ = (1 - e/d) × 100; for slope Inhibition 2 = (d - e)/(c - e) × 100%.

the more severe grades of work. The average sympathetic component of slope of the work-heart rate relationship averaged 38% in the experiments of Table 3, with considerable variation between subjects. The latter may account for the fact that the average sympathetic component of slope based on the peak inhibition value in the oral dose experiments in seven other subjects was somewhat lower, about 26%. At HR_{75} , the vagal component became small and the sympathetic component large (Figure 8), in agreement with the findings by others (e.g., Robinson *et al.*, 1966; Carruthers *et al.*, 1976).

In contrast to the conclusions of the present study Carruthers *et al.* (1976) consider that the small magnitude of vagal activity at high levels of exercise results in more accurate assessment of sympathetic inhibition after β -adrenoceptor blockade. They determined the 'true' sympathetic effect on heart rate by producing maximum β -adrenoceptor blockade in atropinized subjects. This provided a scale for assessing the heart rate changes after submaximal β -adrenoceptor blockade as a percentage of maximum blockade in the atropinized subject (%B). They calculated the correlation coefficients between %B and other measures of inhibition obtained in the absence of atropine including the percentage reduction in exercise heart rate (termed %R) at a high level of exercise and an analogue of slope (termed %I) (Table 4). They found that the correlation coefficient between inhibition estimated as %B and %R was 0.81, but that between %B and %I was only 0.64. This formed the basis of their claim that %R provided a superior method to %I of estimating cardiac sympathetic inhibition. The validity of this claim seems questionable when the actual regression equations are calculated from Table 5 of their paper (Table 4). The intercept of the regression equation relating %R to %B differs significantly from zero, suggesting that the regression equation from their data is not linear (Snedecor & Cochran, 1977). On the other hand, the intercept of the equation relating %B to %I passes through zero, despite the greater scatter

of individual points. In view of the non-linearity of one equation it is difficult to draw conclusions about the superiority or otherwise of %R compared to %I as an index of cardiac sympathetic inhibition from the paper of Carruthers *et al.* (1976).

The present results are in agreement with the conclusion of Carruthers *et al.* (1976), that at high levels of exercise, with maximum β -adrenoceptor blockade, the fall in heart rate is virtually independent of slope and resting value (Figure 8). However, our findings of differential rates of recovery of slope, HR_{50} and of resting rate several hours after giving pindolol suggest that this independence does not hold for submaximal β -adrenoceptor blockade and this probably accounts for the non-linearity of their regression equation.

The rise in heart rate observed with increasing levels of exercise even after combined cardiac sympathetic and parasympathetic blockade has also been observed by others (Jose, Stitt & Collison, 1970; Carruthers *et al.*, 1976). The work of Jose *et al.* (1970) suggests that the rise in body temperature may make an important contribution to the rise in 'intrinsic' heart rate in prolonged exercise.

Thus, the determination in the present study of the work-heart rate relationship from four points and its standardization in terms of each subject's maximum work capacity have probably allowed better characterization of the parameters of the regression line before and after β -adrenoceptor blockade and more accurate evaluation of sympathetic inhibition than has been possible with previous protocols. The regression function is best described by slope and HR_{50} with the latter providing the most accurate assessment of intercept (Snedecor & Cochran, 1977). The effects of β -adrenoceptor blockade on resting heart rate are also of separate clinical interest, but changes in HR_{75} follow the same pattern as the changes in HR_{50} . Because the latter is an outlying single value it is less accurately determined than calculated HR_{50} , which is based on the entire data for each subject.

Table 4 Regression equations from data of Carruthers *et al.* (1976)

Equation	n	SE_b	SE_a	r
% R = 6.01 + 0.239% B	66	0.021	0.46	0.815
% I = -1.11 + 0.450% B	66	0.068	1.44	0.636

Calculated from results in Table 5 of Carruthers *et al.* (1976).

% B = percentage blockade of sympathetic activity
 % R = percentage reduction of control exercise heart rate
 % I = percentage inhibition of 'slope'
 SE_b = standard error of regression coefficient
 SE_a = standard error of intercept
 r = correlation coefficient

Pharmacokinetics and effects of pindolol

The time-concentration curves of pindolol, plasma half-time and apparent volume of distribution are in agreement with previous findings (Hicks *et al.*, 1972; Gugler *et al.* 1974). The value for protein binding of 38% lies between previously reported values (Gugler *et al.*, 1974; Zaagsma & Meems, 1976) and was constant over a large range of plasma drug concentrations. Our bioavailability figure for pindolol of 53% differs from the 100% bioavailability reported by Gugler *et al.* (1974). In both studies different subjects were used for the estimation of AUC after oral and i.v. administration and the discrepancy in estimates arises from differences in AUC following oral administration since the intravenous values for both studies are not significantly different (present study 52.4 ± 10.1 ; Gugler *et al.* 39.1 ± 5.9 ng h ml⁻¹ mg⁻¹). Our values for AUC/dose after oral administration are similar to those reported by Kiger, Lavene, Guillaume, Guerret & Langchamp (1976) following oral administration of 5 mg pindolol (21 ± 2.5 ng h ml⁻¹ mg⁻¹) and slightly lower than those calculated from the data of Gugler *et al.* (1975) after oral administration of 10 mg pindolol (31.7 ng h ml⁻¹ mg⁻¹). The line relating AUC to dose of pindolol in our experiments could be extrapolated to zero, thus resembling results obtained with oxprenolol (Mason & Winer, 1976) but not those with propranolol and alprenolol (Johnsson & Regardh, 1974) where there is no detectable plasma concentration below a threshold dose. The bioavailability results with pindolol suggest the possibility of some 'first pass' metabolism which would be in accord with the drug's high rate of metabolic clearance (Gugler *et al.*, 1974). However, incomplete absorption as an alternative explanation cannot be excluded from our study. This effect is not saturable in the present dose range and is thus of no clinical significance.

The reduction in resting heart rate produced by pindolol in the sitting posture but not while supine is similar to the findings of Aellig (1976) and probably reflects greater cardiac sympathetic activity while sitting. The smaller peak reduction in resting heart rate after high compared with low dose of pindolol is most probably due to masking of β -adrenoceptor blockade by ISA at high doses. This explanation is suggested by the reversal of the paradoxical dose relationship at the time of peak effect, 24 h after taking the drug when plasma pindolol was again low.

The present study has shown an absence of a close relationship between dose and plasma pindolol and effects on resting blood pressure, heart rate and attenuation of the exercise response. Even in the plasma range 5–20 ng/ml inhibition of HR₅₀ was only about 20% below maximum inhibition observed at concentrations of 21–160 ng/ml (Figure 7). This is in contrast to the close relationship between plasma concentration and effect on the exercise response observed by Gugler *et al.* (1975).

The findings of a lower plasma concentration for maximum cardiac β -adrenoceptor blockade with pindolol compared with propranolol (Coltart & Shand, 1970) and the long duration of action despite its short plasma half-life suggests that pindolol may have a higher affinity for the cardiac β -receptor. The difference in plasma protein binding between the two drugs appears to account for a large part of the difference in affinity. Thus from our data the plasma pindolol concentration producing 50% inhibition of the HR₅₀ is less than 5 ng/ml, probably in the vicinity of 2 ng/ml, whilst the corresponding value for propranolol based on the data of Coltart & Shand (1970) is about 12 ng/ml, giving an approximate by six-fold potency ratio. When these values are corrected for the differences in plasma protein binding (approximately 90% for propranolol and 40% for pindolol) both drugs have virtually identical receptor affinities as judged by their identical effectiveness on the beta receptor. This suggests that the relatively low binding to plasma protein of pindolol is an important factor contributing to its greater potency.

Peak inhibition of slope and HR₅₀ were similar at all oral doses, suggesting that at these plasma levels inhibition of sympathetic effects by pindolol was maximal. With resting rate, as discussed earlier, there was a paradoxical maximum inhibition at the lowest dose, probably related to its ISA. Of particular interest was the finding at every dose of unequal rates of recovery of slope and HR₅₀. The complete recovery in slope after 24 h in the presence of clear evidence of residual β -adrenoceptor blockade (isoprenaline experiments) suggests competitive 'breakthrough' of the sympathetic component of the exercise tachycardia at that time. On the other hand, the persistent inhibition of HR₅₀ was entirely accounted by sustained reduction in resting heart rate at these relatively low degrees of β -adrenoceptor blockade. This is of clinical importance in view of the implied reduction in cardiac oxygen requirements and continuing benefits for patients with angina. It should be noted that the factors underlying the sustained reduction in HR₅₀ would not be apparent in the method of analysis advocated by Carruthers *et al.* (1976).

Our findings help to reconcile the differences in the duration of sympathetic inhibition after pindolol reported by Gugler *et al.* (1975) on the one hand, and by Aellig (1976) on the other. Thus Aellig (1976) used a parameter analogous to HR₅₀ and observed prolonged inhibition after pindolol. After 8 h he observed that there was still 85% of peak inhibition, in good agreement with the present finding of 79% at 7 h. In addition, Aellig's figure of 36% of peak inhibition after 24 h is in good agreement with our observed value of 31%. Gugler *et al.* (1975) used a parameter analogous to slope and observed more rapid recovery. After 6 h 53% of peak inhibition was still present, compared with the present figure of 59% after 7 h.

Some of the confusion in the literature has thus resulted from the fact that the two studies based their conclusions on changes in the analogues of one or other of the parameters of the work-heart rate relationship rather than on both, as in the present study. For this reason the use of the present somewhat

more elaborate exercise protocol offers advantages over methods providing less accurate assessment of the work-heart rate relationship.

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