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β-ADRENOCEPTOR BLOCKING ACTIVITY AND DURATION OF ACTION OF PINDOLOL AND PROPRANOLOL IN HEALTHY VOLUNTEERS

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1 The β-adrenoceptor blocking activities of pindolol and propranolol have been investigated in healthy male volunteers.

2 Pindolol was about forty times more potent than propranolol in reducing isoprenaline-induced tachycardia.

3 Pindolol (5 mg) and propranolol (100 mg) were approximately equiactive in reducing exercise-induced tachycardia, 2 h after oral administration.

4 The duration of action of pindolol is significantly longer than that of propranolol; 24 h after pindolol (5 mg), 36 ± 5% of the maximum effect were still present, and after propranolol (100 mg) 16 ± 4% remained.

5 Despite the long duration of action of pindolol, there was no evidence for cumulation during oral administration of 5 mg t.d.s. for 5 days.

Introduction

The therapeutic effectiveness of β-adrenoceptor blocking drugs in hypertension and angina pectoris is attributed to their clearly defined pharmacological action and not to a non-specific effect such as local anaesthetic activity (Prichard, Aellig & Richardson, 1970; Prichard, 1974; Simpson & Waal-Manning, 1970).

Their potential therapeutic value in patients can therefore be estimated by pharmacological studies in normal human volunteers. Their potency as β-adrenoceptor blocking agents in different tests and also their duration of action in these tests can be evaluated under strict experimental conditions. Efficacy and the duration of action of their therapeutic effect in patients can, of course, not be predicted, but the activity and the duration of action of different drugs can be compared.

In the study reported here, the β-adrenoceptor blocking activities of pindolol (LB 46, Visken®) and propranolol (Inderal®) (Figure 1) have been compared on isoprenaline-induced tachycardia. Their duration of action was evaluated on exercise-induced tachycardia only, since it was considered that an exercise test would better resemble the physiological stimulus leading to the attack in patients with angina pectoris. An abstract of the results has been published previously (Aellig, 1973). In view of the fact that pindolol had previously been shown to have a long duration of action (Aellig & Saameli, 1973; Olsson & Varnauskas, 1973), an additional experiment was carried out in a group of normal volunteers who received pindolol (5 mg) three times a day for 5 days to see whether a cumulative effect would occur under a normal therapeutic dosage schedule.

Method

All experiments were carried out in healthy male volunteers after full explanation of the experimental procedures involved.

Heart rate was measured from the ECG and blood pressures were taken with a sphygmomanometer by an observer not informed about the treatment given. Pindolol (Visken) and propranolol (Inderal) were administered as the marketed preparations.

β-adrenoceptor blocking potency (isoprenaline-induced tachycardia) and effects on resting heart rate

This study was performed in three volunteers with a mean age of 26 years (range 24 to 28 years) and a mean weight of 65 kg (range 64 to 67 kg). Resting heart rate was measured in the supine position and after at least 5 min sitting erect on

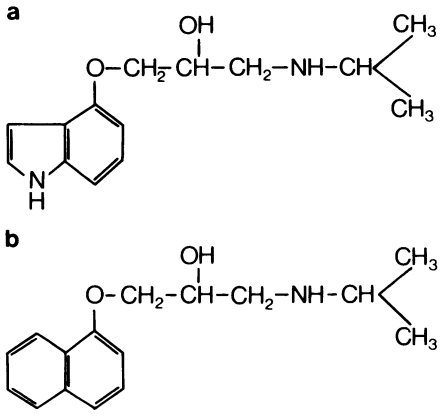

Figure 1 Structural formulae of the β-adrenoceptor blocking drugs investigated, a pindolol; b propranolol.

the cycle ergometer before and 1 and 2 h after administration of the drug under test or placebo.

A solution of isoprenaline hydrochloride was infused into a left forearm vein of the subject resting in the supine position. The starting dose of 2 μg/min was doubled every 5 min until a heart rate of at least 120 beats/min was reached. Isoprenaline infusions were given before and 1 and 2 h after oral administration of a β-adrenoceptor blocking drug or placebo. Higher starting doses were used after the β-adrenoceptor blocking drugs.

From the isoprenaline dose-response curves obtained, the dose of isoprenaline required to increase heart rate to 120 beats/min was determined for each subject before and 1 and 2 h after each dose of the drug under test.

The following doses were administered: pindolol (1, 2.5 and 5 mg) and propranolol (40 and 80 mg). The subjects received all doses and placebo in randomized order on different days with an interval of at least 1 week between two experiments.

Duration of action (exercise-induced tachycardia)

These experiments were carried out in five volunteers with a mean age of 26 years (range 24 to 29 years) and a mean weight of 67 kg (range 64 to 76 kg). Exercise tests on a cycle ergometer with a work load of 150 W for 3 min were performed twice, at hourly intervals, before and 1, 2, 4, 6, 8 and 24 h after the oral administration of pindolol (5 mg) or propranolol (100 mg). All subjects received both drugs in random sequence with an interval of at least 1 week between the two experiments.

Repeated administration of pindolol

Four volunteers with a mean age of 24 years (range 23 to 26 years) and a mean weight of 80 kg (range 66 to 100 kg) were treated with oral doses of pindolol (5 mg) t.d.s. for 5 days. The drug was administered at 08.00 h, 14.00 h and 20.00 h and exercise tests (150 W, 3 min) were carried out before and 1, 2, 3, 4 and 6 h after the morning dose; on days 1 and 5, additional tests were carried out 1, 2 and 3 h after the afternoon dose.

In order to ascertain that higher doses of pindolol would produce a greater reduction in exercise-induced tachycardia than 5 mg and therefore that the above experiment would reveal a possible cumulative effect, an additional study was carried out in six volunteers. Their mean age was 25 years (range 23 to 29 years) and their mean weight 66 kg (range 57 to 76 kg). They received oral doses of pindolol (5 mg and 10 mg) in randomized order on 2 different days with an

Table 1 Resting heart rate, supine and sitting on the cycle ergometer, before and after β-adrenoceptor blocking drugs or placebo (mean ± s.e. mean, $n = 3$)

	Resting Heart rate (beats/min)					
	Pindolol (1 mg)		*Pindolol (2.5 mg)*		*Pindolol (5 mg)*	
	Supine	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*
0 h	77 ± 5	89 ± 4	81 ± 4	88 ± 2	78 ± 5	82 ± 4
1 h	75 ± 3	80 ± 2	79 ± 4	78 ± 1	81 ± 2	76 ± 2
2 h	82 ± 4	82 ± 4	85 ± 4	84 ± 2	83 ± 1	83 ± 3
	Propranolol (40 mg)		*Propranolol (80 mg)*		*Placebo*	
	Supine	*Sitting*	*Supine*	*Sitting*	*Supine*	*Sitting*
0 h	83 ± 3	93 ± 5	79 ± 2	92 ± 3	81 ± 1	89 ± 3
1 h	72 ± 3	77 ± 1	72 ± 2	82 ± 1	77 ± 4	84 ± 2
2 h	77 ± 5	80 ± 3	77 ± 4	87 ± 3	81 ± 4	86 ± 5

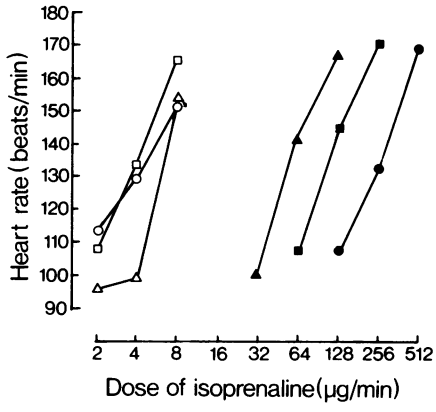

Figure 2 Heart rate (beats/min) during isoprenaline infusions before (open symbols) and 2 h after (closed symbols) oral administration of pindolol (△, ▲ 1 mg; □, ■ 2.5 mg; ○ ● 5 mg) in subject 1.

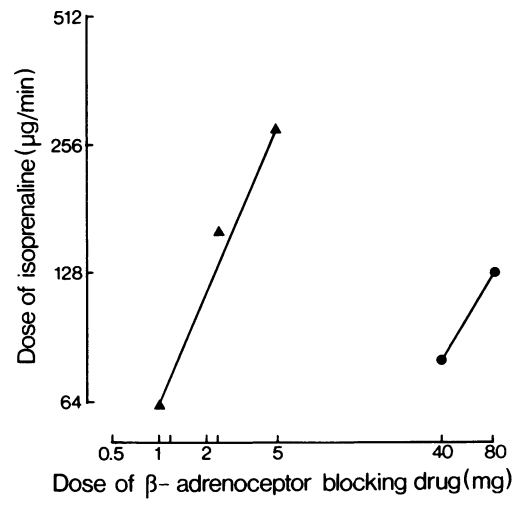

Figure 3 Dose of isoprenaline (μg/min) required to increase heart rate to 120 beats/min, 2 h after oral administration of propranolol (●) or pindolol (▲). The results are the means from three volunteers. Individual values are given in Table 2.

interval of at least 1 week. Exercise tests (150 W, 3 min) were carried out at hourly intervals twice before and three times after drug administration.

Results

Effects on resting heart rate

The effects of the two drugs and placebo on resting heart rate in the supine position and sitting erect on the cycle ergometer are shown in Table 1. In the sitting position, both β-adrenoceptor blocking drugs produced reductions in heart rate, which are greater after propranolol (40 mg) than after pindolol. In the supine position pindolol produced slight increases in resting heart rate whereas propranolol again reduced heart rate.

Isoprenaline antagonism

Increasing doses of each of the β-adrenoceptor blocking drugs led to dose-dependent, parallel shifts of the dose-response curve for isoprenaline (Figure 2); administration of placebo resulted in

Table 2 Dose of isoprenaline (μg/min) required to increase heart rate to 120 beats/min before and after oral administration of the β-adrenoceptor blocking drugs and placebo.

	Dose of isoprenaline (μg/min)								
	Pindolol (1 mg)			*Pindolol (2.5 mg)*			*Pindolol (5 mg)*		
	0 h	*1 h*	*2 h*	*0 h*	*1 h*	*2 h*	*0 h*	*1 h*	*2 h*
Subject 1	5.2	69	44	2.7	100	80	2.7	191	175
2	5.0	97	65	5.3	184	147	4.8	270	388
3	6.0	36	89	5.8	152	279	5.8	175	274
Mean	5.6	67	66	4.6	146	169	4.4	212	279
s.e. mean	0.2	14	11	0.8	20	48	0.7	24	50
	Propranolol (40 mg)			*Propranolol (80 mg)*			*Placebo*		
	0 h	*1 h*	*2 h*	*0 h*	*1 h*	*2 h*	*0 h*	*1 h*	*2 h*
Subject 1	2.0	59	38	3.2	38	79	4.1	3.9	2.0
2	4.6	97	82	7.0	208	181	6.3	5.1	5.0
3	4.6	152	128	3.1	108	117	3.3	4.8	4.8
Mean	3.7	103	83	4.4	118	126	4.6	4.6	4.0
s.e. mean	0.7	22	21	1.0	40	24	0.7	0.3	0.8

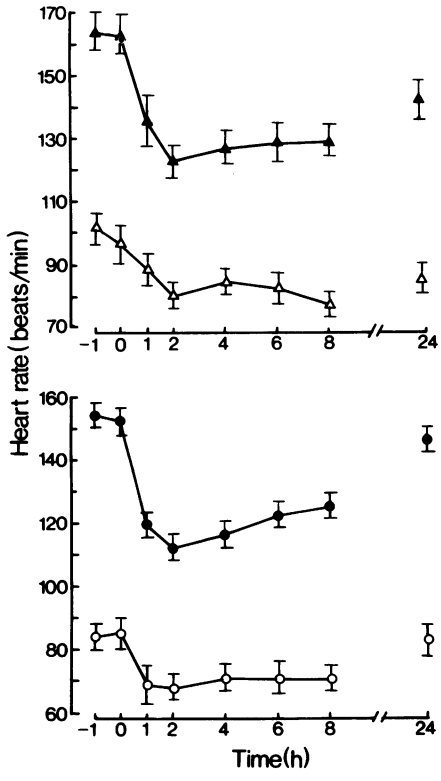

Figure 4 Heart rate before (open symbols) and at the end of 3 min exercise (closed symbols) on the cycle ergometer (150 W) before and after oral administration of pindolol (△, ▲ 5 mg) or propranolol (○, ● 100 mg) (mean ± s.e. mean, $n = 5$).

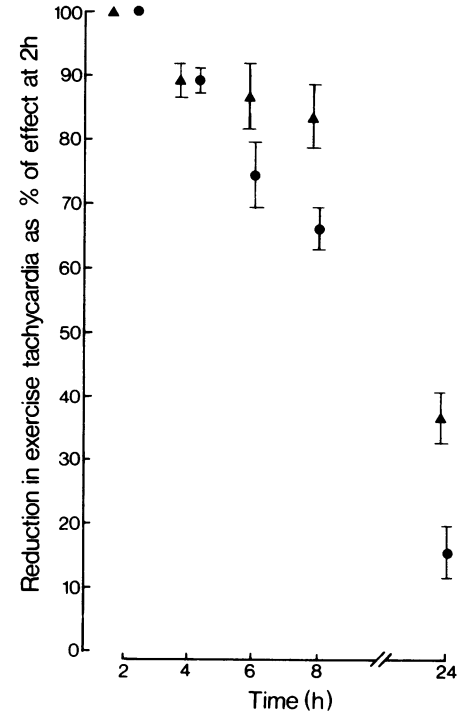

Figure 5 Reduction of exercise-induced tachycardia (150 W, 3 min) expressed as a percentage of the effect at 2 h (mean ± s.e. mean, $n = 5$). The differences between pindolol (▲) and propranolol (●) were statistically significant after 8 h and after 24 h ($P < 0.05$, paired t-test).

little change. The doses of isoprenaline required to increase heart rate to 120 beats/min (Table 2) were plotted against the corresponding dose of the drug under test (Figure 3) and the relative potencies of the drugs calculated. Two hours after administration, pindolol was found to be approximately forty times more potent than propranolol.

Exercise on the cycle ergometer and duration of action

Both drugs produced a marked reduction in exercise-induced tachycardia with a maximum effect 2 h after administration (Figure 4). At this time, heart rate measured at the end of exercise was reduced by 42 beats/min after pindolol (5 mg) and 41 beats/min after propranolol (100 mg). Two hours after oral administration, pindolol (5 mg) and propranolol (100 mg) are therefore equiactive in this test. A comparison after 8 h and after 24 h, however, revealed that at these times, exercise-induced tachycardia was reduced to a greater extent after pindolol than after propranolol. Figure 5 shows reduction in heart rate at the end of exercise 4, 6, 8 and 24 h after drug administration expressed as a percentage of the effect obtained at 2 hours. The differences between pindolol and propranolol are statistically significant after 8 h and after 24 h ($P < 0.05$, paired t-test).

Figures 6 and 7 show systolic and diastolic blood pressure before and after administration of the β-adrenoceptor blocking drugs. The results indicate that after both drugs there was a slight reduction in resting blood pressure, but a much greater and statistically significant fall in systolic blood pressure at the end of exercise. There were no relevant changes in diastolic blood pressure at the end of exercise.

In an additional experiment, six volunteers received a placebo and exercise tests were

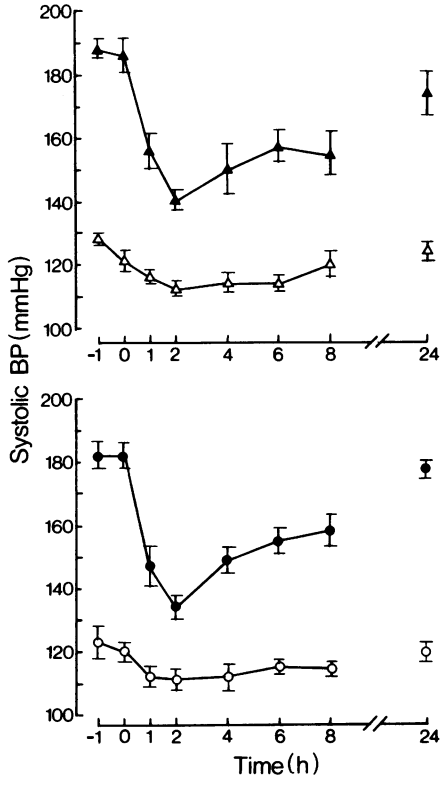

Figure 6 Systolic blood pressure before (open symbols) and at the end of 3 min exercise (closed symbols) on the cycle ergometer (150 W) before and after oral administration of pindolol (△, ▲ 5 mg) or propranolol (○, ● 100 mg) (mean ± s.e. mean, $n = 5$).

performed at the same times as in the main study. Neither resting heart rate nor heart rate at the end of exercise showed any relevant changes throughout the period of observation.

Repeated administration of pindolol

Heart rate at the end of exercise (Table 3) was reduced by 34 beats/min 2 h after the first dose of pindolol. After 6 h, i.e. before the administration of the second dose, 73% of the activity of the first dose was still present, but 2 h after the second dose, no further reduction in exercise-induced tachycardia had occurred.

On the second day before drug administration, i.e. 12 h after the last dose of the first day, exercise-induced tachycardia was still reduced by 20 beats/min. The values obtained after the administration of pindolol were, however, not

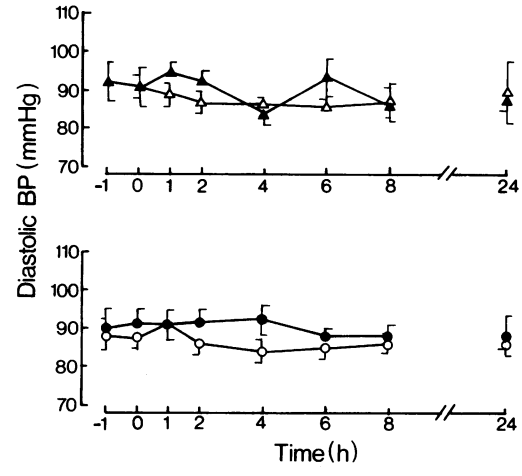

Figure 7 Diastolic blood pressure before (open symbols) and at the end of 3 min exercise (closed symbols) on the cycle ergometer (150 W) before and after oral administration of pindolol (△, ▲ 5 mg) or propranolol (○, ● 100 mg) (mean ± s.e. mean, $n = 5$).

lower than at corresponding times on the first day. Similar results were obtained on the 3rd, 4th and 5th day of the experiment.

In the experiments to compare the effects of 5 mg and 10 mg pindolol, mean exercise-induced tachycardia before the administration of the drug was 146 beats/min in both instances. One hour after the drug, tachycardia was reduced to a mean of 120 and 119 beats/min respectively and after 3 h to 118 and 112 beats/min respectively. The differences between the results after 5 mg and 10 mg pindolol were statistically significant after 2 h and after 3 h ($P < 0.01$, paired t-test).

Although 12 h after a single oral dose of pindolol (5 mg) about 2/3 of the maximum β-adrenoceptor blocking activity was still present, there was no evidence for a cumulative effect following oral administration of 5 mg t.d.s. for 5 days.

Discussion

It is interesting to note that pindolol, a drug with intrinsic sympathomimetic activity (Saameli, 1972) produced slight increases in resting heart rate when the subjects were resting supine, i.e. when sympathetic tone was very low, but that pindolol, like propranolol, but to a lesser extent, reduced resting heart rate in the sitting position when sympathetic tone is higher.

Hill & Turner (1969) compared the effects of pindolol and propranolol in inhibiting tachycardia due to isoprenaline inhalation and tachycardia due to exercise on the bicycle ergometer. They found that pindolol was weight for weight about twenty to forty times more potent than propranolol. In the present study, pindolol was about forty times more potent than propranolol in inhibiting isoprenaline-induced tachycardia and about twenty times more potent in inhibiting exercise-induced tachycardia. The results therefore indicate that there is a difference in the potency ratio for pindolol and propranolol in the two tests used to quantitate β-adrenoceptor blockade in man.

The results also demonstrate that not only exercise-induced tachycardia, but also exercise-induced increase in systolic blood pressure showed a marked and long lasting reduction after both β-adrenoceptor blocking drugs. A comparison between the results obtained 1 and 2 h after oral administration of the two drugs (Table 1) shows that with lower doses (pindolol (1 mg and 2.5 mg) and propranolol (40 mg)) the maximum effect is reached after 1 h, whereas after the highest doses (pindolol (5 mg) and propranolol (80 mg)) it takes 2 h to reach the maximum effect.

The duration of action of pindolol (5 mg) was found to be considerably longer than that of propranolol (100 mg). A long duration of action for pindolol was first reported by Saameli (1972) who observed in experiments in the anaesthetized dog that 5.25 h after a dose of pindolol (16 μg/kg) i.v. more than two thirds of the maximum effect was still present, whereas at the same time, after an equiactive dose of propranolol (256 μg/kg), only about one quarter of the maximum activity was left. Olsson & Varnauskas (1973) found that in healthy volunteers, 24 h after an oral dose of pindolol (5 mg), β-adrenoceptor blockade could still be observed.

Our experiments show that 24 h after pindolol (5 mg) and propranolol (100 mg), a β-adrenoceptor blocking effect could still be demonstrated for both drugs. Whereas for propranolol, 16% of the maximum effect were left at that time, for pindolol the activity still present was 36%.

Published data on the elimination half-life of pindolol and propranolol show some variation. The values for oral pindolol were found to be between 3.5 h (Gugler, Herold & Dengler, 1974) and 4 h (Turner & Peel, 1972); for oral propranolol, between 2.5 h (Paterson, Conolly, Dollery, Hayes & Cooper, 1970) and 3.2 h (Shand, Nuckolls & Oates, 1970). It was shown that the pharmacological activity, measured in terms of a reduction in exercise-induced tachycardia, for practolol (Kumana & Shaw, 1973; Smith, 1973)

Table 3 Heart rate sitting on the cycle ergometer before exercise and at the end of 3 min exercise (150 W) during oral administration of pindolol (5 mg) t.d.s. for 5 days at 08.00 h, 14.00 h, 20.00 h each day (mean ± s.e. mean, n = 4).

	Heart rate (beats/min)				
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*
Sitting					
08.00 h	87 ± 3	81 ± 1	82 ± 2	84 ± 1	86 ± 3
09.00 h	80 ± 2	84 ± 2	80 ± 2	85 ± 2	88 ± 2
10.00 h	77 ± 3	84 ± 2	81 ± 2	84 ± 2	86 ± 1
11.00 h	80 ± 2	81 ± 2	85 ± 2	84 ± 1	87 ± 3
12.00 h	81 ± 3	82 ± 2	82 ± 3	83 ± 1	86 ± 2
14.00 h	84 ± 3	89 ± 2	87 ± 4	90 ± 2	93 ± 1
15.00 h	85 ± 2				91 ± 1
16.00 h	84 ± 2				89 ± 1
17.00 h	86 ± 4				88 ± 1
End of exercise					
08.00 h	153 ± 6	133 ± 3	127 ± 2	128 ± 2	131 ± 1
09.00 h	119 ± 3	128 ± 4	122 ± 2	124 ± 1	126 ± 1
10.00 h	119 ± 3	125 ± 3	121 ± 3	122 ± 2	123 ± 1
11.00 h	121 ± 2	125 ± 3	124 ± 3	124 ± 2	124 ± 1
12.00 h	124 ± 4	127 ± 4	123 ± 3	123 ± 2	125 ± 1
14.00 h	128 ± 3	128 ± 2	128 ± 4	132 ± 3	132 ± 1
15.00 h	126 ± 2				129 ± 1
16.00 h	126 ± 3				127 ± 2
17.00 h	128 ± 3				129 ± 4

and for pindolol (Gugler, Höbel, Bodem & Dengler, 1975) showed an almost linear relationship to the logarithm of the plasma concentration of the drug. This would, of course, only be true for doses on the linear portion of the dose-response curve; with higher doses there is an initial phase during which almost maximal responses persist until blood levels have fallen below a certain level. The data in Figure 5 show that this level was not exceeded with the doses of pindolol (5 mg) and propranolol (100 mg) that were given. There was for both drugs a nearly linear reduction in pharmacological activity per unit of time that began after the maximal effect had been reached. The rates of decline of pharmacological activity for propranolol and pindolol per unit time in the present study showed a ratio of about 3:4, which is comparable to the ratio for the published values for the elimination half-life of the two drugs. It would therefore appear that the difference in the elimination half-lives of the two drugs would explain the difference in their duration of action. There was no cumulation of the effects of pindolol (5 mg) during t.d.s. administration for 5 days. A lack of cumulation of the drug itself was also found in a pharmacokinetic study in man (Aellig & Pacha, unpublished results) in which oral doses of pindolol (5 mg) were administered t.i.d. for 8 days: blood level maxima varied within the same range throughout the treatment period and declined on the last day with the same half-life as after a single oral dose.

If the duration of the pharmacological effects of these drugs in man is relevant for the duration of their therapeutic action, one would anticipate that for pindolol a twice daily dosage should be sufficient. This has been confirmed by Gordon (1975) and Waal-Manning & Wood (1975) who have shown adequate lowering of blood pressure in patients with essential hypertension following administration of pindolol once or twice daily.

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