Pharmacological experiments in healthy volunteers with bopindolol, a long-acting β -adrenoceptor blocking drug with partial agonist activity

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This paper is dedicated to Professor Helmut Kewitz, Berlin, a pioneer of clinical pharmacology in Germany, on the occasion of his 65th birthday.

1 Bopindolol is a potent and specific β -adrenoceptor antagonist with partial agonist activity. In animal experiments it blocks both β_1 - and β_2 -adrenoceptors and possesses a long duration of action. In the present study in healthy volunteers bopindolol was about ten times more potent than pindolol in reducing isoprenaline-induced and exercise-induced tachycardia.

2 In experiments on exercise-induced tachycardia an oral dose of 2 mg produced a near maximum reduction of exercise heart rate, occurring within 2 to 3 h of administration. With higher doses (up to 12 mg) the maximum effect was reached earlier (between 1 and 2 h). The long duration of action of bopindolol observed in animal studies was confirmed in man. Twenty-four hours after 4 and 10 mg bopindolol more than 2/3 of the maximum effect was still present. After 48 h 38% of the maximum effect of 4 mg and 50% of that of 12 mg remained. Even at 72 and 96 h exercise-induced tachycardia was still significantly lowered after both doses of the drug.

3 When bopindolol was administered once daily for 5 days there was a slight increase in the maximum reduction of exercise-induced tachycardia during treatment with 1 mg/day but not with 4 mg/day, which produced a near maximum effect.

Keywords bopindolol β -adrenoceptor blocker partial agonist activity

Introduction

For β -adrenoceptor blocking drugs a long duration of action appears to be of clinical importance since it renders once daily administration possible and thus leads to improved patient compliance (Porter, 1969; General Practitioner Research Group, 1970). This is of special importance not only in a disease like hypertension, where the low incidence of symptoms reduces the incentive for the patients to take their tablets regularly, but also in angina pectoris, where the time course of the therapeutic effect is directly related to the time course of cardiac β -adrenoceptor blockade. Several β -adrenoceptor blocking drugs available exhibit a sufficiently long

duration of action to allow once daily administration for the treatment of hypertension but require more frequent administration to protect anginal patients throughout the day.

A well tolerated drug with a longer duration of action may therefore offer therapeutic advantages. Such a prolonged duration of action has previously been found in animals and man with LL 21-945, a β -adrenoceptor blocking drug, esterified at the side-chain hydroxyl group (Clark *et al.*, 1974; Aellig, 1974). Bopindolol (Sandonorm®), LT 31-200, [4-(2-benzoyloxy-3-tert-butylaminopropoxy)-2-methyl indole hydrogenmalonate], Figure 1) is esterified in a similar

Figure 1 Structural formula of bopindolol.

way. It is a potent and specific β -adrenoceptor antagonist with partial agonist activity, which blocks both β_1 - and β_2 -adrenoceptors (Berthold *et al.*, 1981). In animal experiments *in vivo* bopindolol possesses a long duration of action. In experiments *in vitro* the drug requires a prolonged contact with the tissues before maximum β -adrenoceptor blockade is reached, suggesting that the molecule itself is devoid of β -adrenoceptor blocking activity and that the pharmacological effect is produced by a metabolite formed after hydrolysis of the benzoylester linkage at position 2 of the propranolamine side chain (Berthold *et al.*, 1981).

In the experiments reported here the β -adrenoceptor blocking activity and time course of action of bopindolol were investigated after single and repeated oral doses in healthy male volunteers. Some of the results have been previously reported at a meeting of the British Pharmacological Society and published in abstract form (Aellig, 1982).

Methods

The study was carried out in healthy male volunteers who gave their written informed consent after full explanation of the experimental procedure involved. In experiments in which cardiac β -adrenoceptor blockade was studied by assessing effects on exercise-induced tachycardia the workload on the bicycle ergometer was determined individually before the experiment proper, so as to produce a heart rate between

150 and 170 beats/min in the untreated volunteer after 3 min exercise. Heart rate (determined from the ECG) of the subject sitting on the bicycle ergometer was measured before (mean of the last 3 min before starting exercise) and at the end of 3 min exercise (mean of the last 15 s of exercise). In all experiments in which various single doses of the drugs were studied, there was an interval of at least 1 week between two administrations.

Effects of 0.5 mg and 1 mg bopindolol and 5 mg and 10 mg pindolol orally on isoprenaline- and exercise-induced tachycardia

Six subjects with a mean age of 27 ± 1 years (mean $\pm$ s.e. mean) and a mean body weight of 74.4 ± 4 kg received oral doses of 0.5 and 1 mg bopindolol and 5 and 10 mg pindolol in randomised order. Exercise tests on a bicycle ergometer, as described above, and isoprenaline infusions were carried out before and 2 and 4.5 h after drug administration. A solution of isoprenaline hydrochloride was infused into a left forearm vein of the subject resting in the supine position. The starting dose of $2 \mu\text{g}/\text{min}$ was doubled every 5 min until a heart rate of 120 beats/min was reached. Higher starting doses were used after administration of the β -adrenoceptor blocking drugs. From the isoprenaline dose-response curves the dose of isoprenaline required to increase heart rate to 120 beats/min was determined, as described previously (Aellig, 1976).

Dose-response relationship of oral doses from 0.5 to 10 mg in comparison with 5 and 15 mg pindolol on exercise-induced tachycardia

Six volunteers with a mean age of 27 ± 1 years and a mean body weight of 75 ± 4 kg received oral doses of 0.5 and 2 mg of bopindolol and 5 and 15 mg of pindolol in randomised order. In a second study, after these low doses had been well tolerated in all subjects, doses of 4 and 10 mg of bopindolol were given in this order to the same volunteers. Exercise tests were carried out before and 1, 2, 3, 4, 6 and 24 h after oral drug administration.

Prolonged observation of the effects of oral doses of 4 and 12 mg on exercise-induced tachycardia

After initial studies had shown a long duration of action of bopindolol, oral doses of 4 and 12 mg bopindolol and placebo were administered in randomised order to another group of 6 volunteers with a mean age of 31 ± 2 years and a mean body weight of 69 ± 2 kg. Exercise tests on the

bicycle ergometer were carried out before and 1, 2, 3, 4, 24, 48, 72, 96 and 168 h after drug administration.

Daily oral doses of 1 and 4 mg bopindolol for 5 days

A further experiment was carried out in six volunteers with a mean age of 26 ± 1 years and a mean body weight of 75 ± 4 kg, in order to find out whether a cumulation of the effect occurs during repeated daily administration. Doses of 1 mg and 4 mg bopindolol were administered once daily for 5 days to all subjects in randomised order, with an interval of 9 drug-free days between the two treatment periods.

Results

All doses of bopindolol administered in these studies were well tolerated by the subjects.

Effects of 0.5 mg and 1 mg bopindolol and 5 mg and 10 mg pindolol orally on isoprenaline-induced and exercise-induced tachycardia

As would be expected of β -adrenoceptor antagonists, both pindolol and bopindolol produced a marked reduction in exercise-induced tachycardia, maximum effects occurring 2 h after administration (Table 1). At this time the effect of 0.5 mg bopindolol was about the same as that of 5 mg pindolol, whereas 1 mg bopindolol was slightly more active than 10 mg pindolol. At 2 h bopindolol was therefore about 10 times more potent than pindolol in reducing exercise-induced tachycardia.

Both drugs produced a dose-dependent parallel shift of the dose response curves for isoprenaline-induced heart rate increases, typical of a competitive antagonism. The dose of isoprenaline required to increase the heart rate to 120 beats/min (Table 2 and Figure 2) was markedly increased by both drugs and bopindolol was found to be approximately 10 times more potent than pindolol when values 2 h after oral administration are considered.

Dose-response relationship of oral doses from 0.5 to 10 mg in comparison with 5 and 15 mg pindolol on exercise-induced tachycardia

The results of these experiments confirm that bopindolol is about 10 times more potent than pindolol (Figure 3). The maximum effect of equipotent doses of bopindolol tended to occur somewhat later than that of pindolol. The onset

Table 1 Heart rate sitting on the bicycle ergometer before and after 3 min exercise before and after oral administration of bopindolol or pindolol (beats/min, mean $\pm$ s.e. mean, $n = 6$)

	Bopindolol		Pindolol	
	0.5 mg	1 mg	5 mg	10 mg
<i>Sitting</i>				
0 h	80 $\pm$ 2	85 $\pm$ 4	82 $\pm$ 5	82 $\pm$ 3
2 h	72 $\pm$ 3	76 $\pm$ 3	75 $\pm$ 2	75 $\pm$ 2
4.5 h	75 $\pm$ 1	76 $\pm$ 2	80 $\pm$ 2	77 $\pm$ 2
<i>End of exercise</i>				
0 h	156 $\pm$ 4	163 $\pm$ 4	163 $\pm$ 3	162 $\pm$ 3
2 h	129 $\pm$ 3	124 $\pm$ 3	127 $\pm$ 3	123 $\pm$ 3
4.5 h	131 $\pm$ 3	126 $\pm$ 2	133 $\pm$ 3	130 $\pm$ 3

of action of equipotent β -adrenoceptor blocking doses of bopindolol was therefore somewhat slower than that of pindolol. Similarly, the duration of action of bopindolol was longer than that of pindolol. Between 6 and 24 h after administration exercise-induced heart rate rose by 17 beats/min after both doses of pindolol but only 10 and 12 beats, respectively, after 0.5 and 2 mg bopindolol. From Figure 4, which shows the results obtained with all four doses of bopindolol, it is evident that as little as 2 mg produced a near maximum effect. After the higher doses, however, the maximum was reached earlier and the effect continued for an even longer period. Twenty-four hours after the 10 mg dose most of the effect was still present.

Both bopindolol and pindolol exerted only a small influence on resting heart rate, a feature typical of β -adrenoceptor blockers exerting partial agonist activity.

Prolonged observation of the effects of oral doses of 4 and 12 mg on exercise-induced tachycardia

An increase in the dose of bopindolol from 4 to 12 mg did not produce a greater maximal reduction of exercise-induced tachycardia (Figure 5). Twenty-four hours after both doses more than 2/3 of the maximum effect was still present. After 48 h 38% of the maximum effect of 4 mg and 50% of that of 12 mg were still present. Even after 72 and 96 h exercise-induced tachycardia was still significantly reduced by either dose of the drug.

Effects of daily oral doses of 1 and 4 mg bopindolol for 5 days

Heart rate at rest and at the end of exercise before and on days 1, 3 and 5 during treatment

Table 2 Dose of isoprenaline ($\mu\text{g}/\text{min}$) required to increase heart rate to 120 beats/min before and after oral administration of bopindolol and pindolol (mean $\pm$ s.e. mean, $n = 6$)

Time (h)	Bopindolol		Pindolol	
	0.5 mg	1 mg	5 mg	10 mg
0	4.7 ± 0.8	4.0 ± 0.5	4.9 ± 0.6	3.7 ± 0.4
2	186 ± 58	468 ± 150	205 ± 38	412 ± 60
4.5	107 ± 33	358 ± 96	132 ± 22	239 ± 45

Figure 2 Dose of isoprenaline required to increase heart rate to 120 beats/min 2 h after oral administration of 0.5 mg and 1 mg bopindolol (■) and 5 mg and 10 mg pindolol (▲) (mean, $n = 6$).

with bopindolol in doses of 1 mg and 4 mg administered once daily are shown on Figure 6. During treatment with 1 mg bopindolol daily the maximum reduction of exercise-induced tachycardia increased somewhat from day 1 to day 5. No increase was observed with 4 mg bopindolol daily. No such increase was seen with the higher dose, because it produced a near maximum reduction of exercise-induced tachycardia even

after the first administration. Exercise heart rate values at times earlier or later than those of the maximum effect (which could have decreased with higher doses) show only a slight further reduction during the 5 days of treatment. At no time on the fifth day did the effect of 1 mg reach that observed after the first single dose of 4 mg.

Discussion

The pharmacological studies with bopindolol reported here show that, on a weight for weight basis, bopindolol is one of the most potent β -adrenoceptor blocking drugs available. An oral dose of 1 mg produces about the same cardiac β -adrenoceptor blockade—measured by the inhibition of isoprenaline-induced and exercise-induced tachycardia—as 10 mg pindolol. In similar tests the activity of 5 mg pindolol equals that of about 100 mg propranolol (Aellig, 1976).

From the dose-response curve study with bopindolol on exercise-induced tachycardia it is evident that an oral dose of 2 mg produces a near maximum effect. With higher doses, this maximum is reached earlier, and the effect was maintained for an even longer time. Twenty-four hours after 10 mg most of the effect was still present.

Figure 3 Exercise-induced tachycardia before and after oral administration of bopindolol ($\circ$ 0.5 mg, $\bullet$ 2 mg) and pindolol (Δ 5 mg, $\blacktriangle$ 15 mg (mean, $n = 6$)).

Figure 4 Heart rate at rest and at the end of 3 min exercise before and after oral administration of bopindolol (mean, $n = 6$).

The long duration of action of bopindolol observed in the animal studies was thus confirmed in man. The experiments with prolonged observation up to 7 days after dosing show that 48 h after 4 mg about 40% of the maximum effect was still present and about half of that of the 12 mg dose. Even after 72 h and after 96 h exercise-induced tachycardia was still significantly reduced. The duration of action of bopindolol is therefore longer than that of most other β -adrenoceptor blocking drugs apart perhaps from nadolol and FM 24 (1(2-exo-bicyclo [2,2,1] hept-2-yl phenoxy-3 [(1-methyl/ethyl)amino]-2 propanol) (Dollery *et al.*, 1983). Bopindolol, however, differs from nadolol and FM 24 in that it possesses partial agonist activity. This is

evident from the relatively small influence on resting heart rate, suggesting that bopindolol produces only small reductions of resting cardiac output.

Following oral administration the onset of action of equipotent β -adrenoceptor blocking doses of bopindolol is slower than that of pinidolol or other β -adrenoceptor blocking drugs. Furthermore, in studies in which the drug was administered intravenously (Aellig *et al.*, 1985) despite the fact that a marked effect was observed within 30 min, the maximum effect was not attained until 3 h after injection. This supports the hypothesis of a metabolic transformation of the parent compound into the active drug, hydrolysed bopindolol, in the body. In a pharmaco-

Figure 5 Heart rate at rest and at the end of 3 min exercise before and after oral administration of bopindolol (● 4 mg, ▲ 12 mg) or placebo (■) (mean $\pm$ s.e. mean, $n = 6$).

Figure 6 Heart rate at rest and at the end of 3 min exercise before and during treatment with bopindolol once daily (● 1 mg, ▲ 4 mg) for 5 days (mean $\pm$ s.e. mean, $n = 6$).

kinetic study a relatively long invasion half life of the active compound was found (Aellig *et al.*, 1985). In the same study it was found also that even after intravenous drug administration the maximum plasma concentration of the active metabolite is reached only about 2 h after the injection. The elimination of hydrolysed bopindolol was found to occur with an α phase of about 4 h and a β phase of 8 h.

Despite the rather long duration of action of bopindolol there is no evidence for a clinically relevant accumulation of the effect during chronic oral therapy. This has been confirmed in a pharmacokinetic and pharmacodynamic steady state study by Platzer *et al.* (1984) who, during treatment for 2 weeks, found no evidence for a cumulation of either the plasma levels of hydrolysed bopindolol or of the pharmacodynamic effect measured by the reduction of exercise-induced tachycardia.

The long duration of action of bopindolol found in these experiments in healthy volunteers

has been confirmed in other studies in healthy volunteers (Turner *et al.*, 1984) and in therapeutic studies in patients with essential hypertension (van Brummelen *et al.*, 1983; Hulthén *et al.*, 1983); and angina pectoris (Nyberg, 1982). In the study in healthy volunteers reported by Turner *et al.* (1984) the rise in plasma renin produced by head-up tilting was markedly reduced during the period of observation of 24 h.

The pharmacological results reported here, together with the published results of therapeutic studies, therefore suggest that bopindolol is a highly potent β -adrenoceptor blocking drug with a long duration of action, potentially suitable for a once-a-day administration not only in patients with hypertension but also for the treatment of angina pectoris.

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