β -ADRENOCEPTOR BLOCKING EFFECTS AND PHARMACOKINETICS OF BETAXOLOL (SL 75212) IN MAN

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1 The pharmacological effects and the pharmacokinetics of betaxolol (SL 75212), a new β -adrenoceptor blocking agent, were compared with those of propranolol and a placebo in a double-blind trial involving six healthy volunteers.

2 Heart rate (HR), myocardial contractile force (MCF), systolic blood pressure (SBP) and peak expiratory flow rate (PEFR) were measured at rest and during vigorous exercise before and at intervals up to 25 h after oral administration of the drugs. In addition, plasma renin activity (PRA) at rest and blood levels of betaxolol and propranolol were determined.

3 Betaxolol proved to be a potent and long-lasting β -adrenoceptor blocking drug, devoid of intrinsic β -sympathomimetic activity. Its β -adrenoceptor blocking action was shown to be four-fold that of propranolol at the cardiac and renal levels and to last at least 25 h after drug intake.

4 The peak blood level of betaxolol was reached 2 to 4 h after its administration, the first-pass loss is likely to be low and the half-life is 12.3 h. These pharmacokinetic data are perfectly consistent with the long duration of the pharmacological effects of betaxolol in man.

Introduction

($\pm$)-1-(isopropylamino)-3-[*p*-(2-cyclopropyl methoxyethyl)-phenoxy]-2-propanol, or betaxolol (SL 75212), is a new β -adrenoceptor blocking drug, the pharmacological properties of which have been investigated in animals (Boudot, Cavero, Fenard, Lefèvre-Borg, Manoury & Roach, 1979). These studies have shown that betaxolol is a potent (3 to 10 times as potent as propranolol when taken orally and equivalent intravenously), long-acting, cardio-selective β -adrenoceptor blocking agent, which appears to be devoid of membrane stabilizing properties and intrinsic sympathomimetic activity. Preliminary pharmacokinetic data in dogs and men (Bianchetti, Gomeni, Kilborn, Morselli, Taylor & Warrington, 1979) indicate that betaxolol has a low initial hepatic extraction when given orally and exhibits long blood and biological half-lives. Thus, betaxolol appears to be of potential value in the treatment of cardiovascular diseases in man on a once daily administration basis.

The present studies were undertaken in order to determine the β -adrenoceptor blocking potency of betaxolol after oral administration in man and to

compare it under double-blind conditions with that of propranolol at the cardiac, pulmonary and renal levels, the parameters investigated being respectively resting and post-exercise heart rate, myocardial contractile force and peak expiratory flow rate and resting plasma renin activity. Furthermore, measurement of betaxolol and propranolol blood levels was performed in order to determine their pharmacokinetic parameters and to look for a possible correlation between these blood levels and the biological activity.

Methods

The trial was conducted with the participation of six healthy volunteers, three male and three female, aged 20–25 years, weighing from 50 to 68 kg, who underwent a complete medical examination to eliminate any possible contra-indication to the administration of β -adrenoceptor blocking drugs. They were given oral doses of betaxolol, propranolol and a placebo in random order at weekly intervals.

Randomization was based on a latin square design under double-blind conditions. None of the subjects was receiving any other medication at the time of the trial, except for two of the three women who were on oral contraceptives.

In view of the results of a brief open preliminary trial, the doses used for the double-blind trial were respectively 20 mg for betaxolol and 80 mg for propranolol.

Parameters investigated

The following parameters were studied before and over a 25 h period following drug intake: heart rate (HR) (measured over 30 s using an ECG) and myocardial contractile force (MCF) [estimated by the systolic time intervals method using an ECG, a carotidogram and a phonocardiogram and measuring the PEPc (pre-ejection period corrected for HR)/LVETc (left ventricular ejection time corrected for HR) ratio] (Weissler, Harris & Schoenfeld, 1968, 1969; Cokkinos, Heimonas, Demopoulos, Haralambakis, Tsartsalis & Gardikas, 1976) to investigate the cardiac β_1 -adrenoceptors; peak expiratory flow rate (PEFR) (mean of five readings using a Wright peak flow meter) to investigate the β_2 -adrenoceptors (Kumana, Marlin, Kaye & Smith, 1974); systolic blood pressure (SBP) measured by means of a mercury sphygmomanometer; plasma renin activity (PRA) (measured by radioimmunoassay according to Ménard, Corvol, Allegrini & Bremiener, 1972) to investigate the juxtaglomerular apparatus β -adrenoceptors. Finally, blood and urinary levels of betaxolol and propranolol, assessed by gas chromatography (see below) were measured in order to determine the pharmacokinetic parameters of the two drugs.

Experimental procedure

The experimental protocol was as follows: after a light breakfast at 07 h 30 min, the volunteer arrived at the laboratory at 08 h 30 min and rested for 45 min. At 09 h 15 min, he (or she) underwent all the control tests (HR, MCF, PEFR, SBP) sitting on a Monark bicycle ergometer, had a blood sample taken (for PRA and blood levels determinations) and was immediately asked to exercise for 3 min at 150 Watts on the ergometer; HR and MCF were again determined during the last 30 s of exercise and PEFR and SBP measured immediately after the end of exercise. The whole sequence lasted approximately 20 min. At 10.00 h, the volunteer was given the drug orally together with 60 ml of water.

The entire sequence consisting of pre-exercise determinations (HR, MCF, PEFR, SBP, PRA and blood levels), 3 min of exercise and post-exercise determinations (HR, MCF, PEFR and SBP) was

then repeated 1, 2, 3, 4, 6, 8, 23 and 25 h after drug intake. In two volunteers, pre- and post-exercise HRs were also determined and blood samples taken 48 and 72 h after drug intake. On the first day, the volunteers were also asked to fill out every hour a questionnaire as to their general tolerance to the drugs. They had a light meal at 12 h 30 min in the laboratory.

Urine was collected 3, 6, 8, 12, 23 and 25 h after drug intake.

No tea, coffee, alcoholic beverages or smoking were allowed during the entire trial period.

Assay of betaxolol and propranolol

Betaxolol was measured by a gas-chromatographic method using a Perkin Elmer 3920 B gas-chromatograph equipped with an electron capture detector. The glass column (2 m $\times$ 3 mm i.d.) was packed with 3% OV-17 on Chromosorb W AW-DMCS. The determination was based on an extraction of betaxolol and its internal standard, propranolol, from blood made alkaline by diethyl ether. After several steps of purification, both compounds were derivatized with heptafluorobutyric anhydride in order to form a fluorinated derivative which could be measured with an electron capture detector (Bianchetti, Ganansia & Morselli, 1979).

The absolute sensitivity of the method was 1 ng/ml of blood. The linearity of the method exceeded 100 ng/ml. Its reproducibility ranged from $\pm 10\%$ for concentrations of 5–10 ng/ml to about ± 5 –8% for values of 15 to 80 ng/ml. Determinations were usually done on 1–2 ml of blood.

Propranolol blood levels were determined by the same method using betaxolol as an internal market. The threshold of detection of propranolol in blood was 1 ng/ml.

Urine betaxolol and propranolol levels were measured by the same method, after dilution with the phosphate buffer if necessary.

Treatment of pharmacokinetic data

The area under blood drug concentration/time curve (AUC) was calculated using a trapezoidal rule. The extrapolation to infinity was made using the slope of the elimination phase curve, applying the equation:

$$AUC = AUC_{t_{25}} + \frac{C_{t_{25}}}{\beta} \quad (1)$$

where $AUC_{t_{25}}$ is the area under blood concentration-time curve from 0 to 25 h, β the terminal exponent of the biexponential curve and $C_{t_{25}}$ the blood drug concentration at time 25 h.

The calculation of the fraction of the dose readily available for the systemic circulation was based on

Figure 1 Heart rate before (lower tracings) and at the end of 3 min exercise (upper tracings) on the cycle ergometer (150 Watts) before and at various times after oral administration of betaxolol (SL 75212) (●, 20 mg), propranolol (▲, 80 mg) and a placebo (○) (mean $\pm$ s.e. mean, $n=6$). Significant difference from pretreatment value: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

the equation of Gibaldi, Boyes & Feldman (1971) modified by Rowlands (personal communication) for the amount excreted unchanged in the urine:

$$F = \frac{Qh \cdot AUC + Ae_{\infty}}{Qh \cdot AUC + Dose} \quad (2)$$

where Qh is the hepatic blood flow (assumed to be the average literature value, i.e. 79.3 l/h) and Ae_{∞} the cumulative amount of drug excreted unchanged in urine.

The estimation of the clearance (Cl) (i.e. the volume of blood cleared from the drug per unit of time) was based on the equation:

$$Cl = \frac{Qh + \frac{Ae_{\infty}}{AUC}}{1 + Qh \cdot \frac{AUC}{Dose}} \quad (3)$$

and the volume of distribution was calculated as:

$$V_d = Cl/\beta$$

The two equations (2) and (3) allow us to estimate parameters such as F and Cl on the basis of the drug concentration data in blood obtained after one single oral administration.

Drugs used

The drugs used were betaxolol hydrochloride (20 mg) and propranolol hydrochloride (80 mg). Doses are expressed in terms of the salts.

Statistical analysis

Statistical analysis of the data was performed by means of the Student's t -test (paired comparisons with pre-drug values for clinical parameters or comparisons between betaxolol and propranolol pharmacokinetic parameters mean values).

Results

Heart rate

Figure 1 illustrates the changes in heart rate measured at rest and after exercise under the influence of betaxolol, propranolol and the placebo.

At rest, betaxolol significantly reduced heart rate 2 h after intake and this effect was maintained for the six following hours. Heart rate was also significantly reduced 2 h after propranolol administration, but afterwards progressively returned to pre-drug values.

Following exercise, both betaxolol and propranolol significantly reduced exercise-induced tachycardia for 8 h, their peak effect occurring after 2 h and being of similar intensity. However, the effect of propranolol, which began slightly earlier than that of betaxolol, had completely disappeared after 23 h, while that of betaxolol was still present and significant. Furthermore, in the two volunteers who were investigated for a larger time after drug intake, the exercise-induced tachycardia was still reduced in both of them after 48 h and in one of them after 72 h (Table 1).

Figure 2 $PEP_c/LVET_c$ ratio before (upper tracings) and at the end of 3 min exercise (lower tracings) on the cycle ergometer (150 Watts) before and at various times after oral administration of betaxolol (SL 75212) (●, 20 mg), propranolol (▲, 80 mg) and a placebo (○) (mean $\pm$ s.e. mean, $n=6$). Significant difference from pretreatment value : * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Myocardial contractile force

Figure 2 illustrates the changes in MCF, estimated by the variations of the $PEP_c/LVET_c$ ratio, induced at rest and after exercise by betaxolol, propranolol and the placebo.

At rest, both betaxolol and propranolol significantly increased the $PEP_c/LVET_c$ ratio, thus decreased MCF, 1 and 2 h after drug intake. This effect was of similar intensity and duration with both drugs. Twenty-three and 25 h after intake of betaxolol or the placebo, $PEP_c/LVET_c$ values were significantly higher than at the same time on the former day, but there was no difference between the values observed under the influence of the three drugs.

After exercise, MCF was not modified by any of the three drugs.

Systolic blood pressure

Figure 3 illustrates the changes in SBP measured at rest and after exercise under the influence of betaxolol, propranolol and the placebo.

At rest, SBP was significantly reduced by propranolol for 3 h and by betaxolol at 3 and up to 8 h.

Following exercise, SBP was significantly decreased by betaxolol and propranolol during the 8 h following drug intake. However, if the peak effect of both drugs was of similar intensity, it occurred earlier (after 2 h) with propranolol than with betaxolol (after 3 h). Later, the effect of betaxolol was more pronounced than that of propranolol and was still present after 23 h, while that of propranolol had disappeared.

Table 1 Post-exercise heart rate values in two subjects before and over a 72 h period following oral administration of betaxolol (20 mg)

	Before betaxolol	Post-exercise heart rate values (beats/min)									
		Time after betaxolol (h)									
		1	2	3	4	6	8	23	25	48	72
Subject 5	160.8	142.9	126.3	126.9	133.9	132.7	133.3	129.0	137.9	147.8	158.7
Subject 6	181.8	150.0	137.3	137.0	140.5	142.9	141.5	138.2	148.9	142.9	169.0

Figure 3 Systolic blood pressure before (lower tracings) and at the end of 3 min exercise (upper tracings) on the cycle ergometer (150 Watts) before and at various times after oral administration of betaxolol (SL 75212) (●, 20 mg), propranolol (▲, 80 mg) and a placebo (○) (mean $\pm$ s.e. mean, $n=6$). Significant difference from pretreatment value: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 4 Changes (in per cent of initial value) in exercise-induced increase in peak expiratory flow rate (PEFR) at various times after oral administration of betaxolol (SL 75212) (●, 20 mg), propranolol (▲, 80 mg) and a placebo (○) (mean $\pm$ s.e. mean, $n=6$). Significant difference from pretreatment value: * $P < 0.05$, ** $P < 0.01$.

Peak expiratory flow rate

Figure 4 shows that during the 3 h period following its oral administration, propranolol induced a reduction in exercise-induced increase in PEFR which was significant after 1 h. No such effect was observed after betaxolol and the placebo.

Plasma renin activity

Both betaxolol and propranolol reduced PRA and inhibited the lunch-induced increase in PRA observed on the placebo day (Figure 5). The reduction in PRA induced by betaxolol lasted up to the twenty-fifth hour following drug intake, while that provoked by

Figure 5 Plasma renin activity before and at various times after oral administration of betaxolol (SL 75212) (●, 20 mg), propranolol (▲, 80 mg) and a placebo (○) (mean $\pm$ s.e. mean, $n=6$). Significant difference from pretreatment value: * $P < 0.05$.

Figure 6 Blood levels at various times after oral administration of betaxolol (SL 75212) (●, 20 mg) and propranolol (▲, 80 mg) (mean $\pm$ s.e. mean, $n=6$).

propranolol was significant only 1 and 2 h after administration and had disappeared after 23 h.

Pharmacokinetics

Figure 6 illustrates the mean blood levels of betaxolol and propranolol over the 25 h period following drug intake. With betaxolol, the levels obtained ranged between 48 and 75 ng/ml for the peak value which occurred between 2 and 4 h after the dose. With propranolol, the levels obtained ranged between 8 and 82 ng/ml at the peak value which was found between 2 and 3 h. Despite the fact that the administered dose of propranolol was four times higher than that of betaxolol, there was no difference between the peak blood levels of the two drugs,

neither was there any difference between the occurrence times of these peak blood levels.

Blood levels of betaxolol could be measured up to 25 h in all subjects and also in both of the volunteers investigated 48 h after drug intake. Blood concentrations of propranolol were detectable until 23 h only in three subjects, but never at 25 h.

The pharmacokinetic parameters of betaxolol and propranolol are reported in Table 2. With betaxolol, the half-life was 12.3 ± 1.1 h (range 9.3–15.8), the fraction F of the dose available for systemic circulation, calculated on the basis of equation (2) was $80.1 \pm 1.7\%$ (range 74.2–85.8) of the administered dose, the clearance was 0.28 ± 0.02 l h⁻¹ kg⁻¹ (range 0.20–0.34) and the volume of distribution was 4.9 ± 0.3 l/kg (range 4.1–6.4). With propranolol, the

corresponding values were 4.1 ± 0.6 h (1.9–6.2), $16.0 \pm 3.2\%$ (5.7–26.0), 1.13 ± 0.06 l h⁻¹ kg⁻¹ (0.95–1.35) and 6.3 ± 0.8 l/kg (3.4–9.3).

Measurement of urinary elimination of both drugs revealed that the amount of the administered dose excreted unchanged was 8.3% (range 3.7–12.4) for betaxolol and 0.98% (range 0.20–2.77) for propranolol.

General tolerance

As a rule, general tolerance to the two drugs was excellent. The only side effects encountered were numbness of hands and feet in two volunteers with betaxolol and propranolol, light exercise dyspnoea in one subject after betaxolol, sweating in one case with betaxolol and drowsiness in two volunteers with propranolol and the placebo.

Discussion

Vigorous exercise has been shown to be an excellent physiological means of inducing intense sympathetic stimulation in man. This is true at the cardiac level where exercise-induced tachycardia and increase in MCF are almost maximal, vagal tone being almost completely abolished (Hicks, Arbab, Turner & Hills, 1972; Gugler, Hobel, Bodem & Dengler, 1975). It is also true at the pulmonary level where post-exercise PEFR values are always greater than pre-exercise ones (Kumana *et al.*, 1974; Marlin, Kumana, Kaye, Smith & Turner, 1975). Thus monitoring of exercise-induced variations in HR, MCF and PEFR before and after administration of β -adrenoceptor blocking agents provides an adequate means of evaluating the cardiac β_1 - and to a lesser extent the pulmonary β_2 -adrenolytic potency of these drugs.

Our results, which confirm experimental pharmacological data (Boudot *et al.*, 1979), demonstrate that in man betaxolol behaves as a potent and long lasting β -adrenoceptor antagonist. Thus, since betaxolol, in

a 20 mg dose, appears to be as effective, in terms of controlling exercise-induced tachycardia, as 80 mg propranolol, the β -adrenoceptor blocking activity in man of the former drug when taken orally appears to be four times as great as that of the latter. Furthermore, it is long-lasting since HR, SBP and PRA remain clearly affected by betaxolol 25 h after administration (HR is even still lowered after 48 h), whereas propranolol's effects have substantially lessened after 8 h and have completely disappeared 23 h after intake.

In our experiments, betaxolol did not affect the exercise-induced increase in PEFR, while propranolol slightly reduced it. The limits of the PEFR method in assessing 'cardioselectivity' in man have clearly been pointed out (McDevitt, 1978; Oh, Kaye, Warrington, Taylor & Wadsworth, 1978) and therefore, if it appears from our experimental data that betaxolol is less active than propranolol on the respiratory tract, one cannot however conclude that, like in animals (Boudot *et al.*, 1979), betaxolol is a 'cardioselective' drug in man. Furthermore, the term 'cardioselective' is certainly not the most suitable for β -adrenoceptor blocking drugs which have little or no action on the bronchi, since all these drugs, betaxolol included, also act on the renal juxtaglomerular apparatus to reduce renin secretion and prevent its post-prandial rise.

As far as the cardiac effects (HR and MCF) of betaxolol and propranolol are concerned, three phenomena should be noted. The first is that both drugs reduce HR and MCF at rest, which confirms, as the animal studies suggested, that betaxolol, like propranolol, is devoid of intrinsic sympathomimetic activity. The second is that even though betaxolol and propranolol lessen the exercise-induced tachycardia, they do not modify the rise in MCF caused by exercise. Since MCF at rest is reduced by both substances, the explanation of this phenomenon is not to be found in either a lack of sensitivity of the method in detecting negative inotropic effects or in their actual absence. But it is likely that, because of an exercise tachycardia which is no longer maximal

Table 2 Comparison between the mean ($\pm$ s.e. mean) values of the pharmacokinetic parameters of betaxolol and propranolol

Drug	Dose (μ g/kg)	Elimination rate constant (h ⁻¹)	Half-life (h)	Apparent bioavailability (%)	Apparent clearance (l h ⁻¹ kg ⁻¹)	Apparent volume of distribution (l/kg)	Area under plasma concentration/time curve (ng ml ⁻¹ h)
Betaxolol	325 $\pm$ 16	0.058 $\pm$ 0.006	12.3** $\pm$ 1.1	80.1** $\pm$ 1.7	0.28** $\pm$ 0.02	4.9 $\pm$ 0.3	971.11** $\pm$ 89.3
Propranolol	1309 $\pm$ 67	0.188 $\pm$ 0.034	4.1 $\pm$ 0.6	16.0 $\pm$ 3.2	1.13 $\pm$ 0.06	6.3 $\pm$ 0.8	207.6 $\pm$ 49.8

** : significantly different from the corresponding propranolol value $P < 0.01$

under β -adrenoceptor blockade, the muscular effort is increased and leads to a raised venous return; the latter thus augments the heart size which may counteract the negative inotropic effects of the drug (Chamberlain, 1966). Lastly, the third phenomenon that has been observed is that if the effects of propranolol on HR and MCF at rest have roughly the same kinetics, those of betaxolol seem more transient on resting MCF than on resting HR, which could possibly mean that the negative chronotropic effect of this drug is more intense and prolonged than its negative inotropic one.

The striking difference observed in our experiments between the duration of action of betaxolol and propranolol appears logical when the evolution of their blood levels and their pharmacokinetic parameters are compared. Two observations can then be made: (1) betaxolol shows a slower clearance than propranolol, and consequently, a longer half-life, and (2) betaxolol is less subject to the phenomenon of first-pass through the liver than propranolol so that a bigger amount of the administered dose is available for systemic circulation.

The other pharmacokinetic parameters seem to be identical. In fact, both drugs are well absorbed from the gastro-intestinal tract and about 95–100% of the dose enters the pre-systemic circulation as shown by radio-labelled techniques used for analysis in our laboratories for betaxolol (Dring & Seevers, personal communication) and by Paterson, Conolly, Dollery, Hayes & Cooper (1970) for propranolol. The velocity of absorption appears to be practically the same for the two drugs since the time at which the peak concentration is reached (about 2–3 h) is approximately identical.

However, there does appear to be a difference between the peak concentrations which vary about ten times for propranolol (range 8–82 ng/ml, see also Shand, Nuckolls & Oates, 1970; Shand, 1974) but only twofold for betaxolol. This result confirms the high first-pass effect of propranolol but suggests a low first-pass effect for betaxolol. In fact we know that other drugs undergoing a high first-pass loss show a large fluctuation in their blood levels because the interindividual variability in the first-pass loss plays a major role in determining the systemic

availability of the drug (Grant, Wilkinson & Shand, 1975).

Our impression has been confirmed by the calculation of the first-pass value. This value was calculated by assuming that hepatic blood flow is relatively constant for all individuals and a mean standard value of 79.3 l/h was used. For propranolol we found that only 16% of the administered dose is available, confirming previous data (Gomeni, Bianchetti, Sega & Morselli, 1977), whereas for betaxolol, 80% of the administered dose is available. The assumed value for hepatic blood flow allows us to calculate the relative bio-availability of one compound relative to the other. However, as the value of about 20% calculated for propranolol is similar to that calculated from data obtained after intravenous administration, it can be assumed that the value of 80% obtained for betaxolol is of the correct order. This means that the amount of drug available for both substances was the same (16 mg) although the administered dose of propranolol was four times higher than that of betaxolol. Propranolol and betaxolol show practically the same value for volume of distribution, which is in agreement with the similarity in blood concentrations at peak time and, if the clearance for the two drugs was also equal, they would show the same kinetic profile. However, the clearance of betaxolol appears to be very different and very much slower than that of propranolol, as indicated by the half-life for betaxolol which is about four times that of propranolol. There is consequently a large difference between the AUCs and this may be due to low first-pass extraction of betaxolol, as recently demonstrated by Bianchetti *et al.* (1979). Finally, the prolonged maintenance of high blood levels with betaxolol, due to its low clearance, is in accordance with the long duration (at least 25 h) of its pharmacological effects (HR, SBP and PRA) in man and suggests that betaxolol could probably be administered on a once daily basis.

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