CARDIOVASCULAR EFFECTS OF SINGLE ORAL DOSES OF THE NEW β -ADRENOCEPTOR BLOCKING AGENT BETAXOLOL (SL 75212) IN HEALTHY VOLUNTEERS

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- 1 The effects of betaxolol (SL 75212), a new β -adrenoceptor blocking agent, on the cardiovascular response to exercise have been studied in six normal subjects after placebo and single oral doses of 5, 10, 20 and 40 mg given double-blind in a randomized sequence.
- 2 All doses reduced exercise heart rate, with a significant reduction persisting to 23h after doses of 20 mg and 40 mg. Systolic blood pressure on exercise was reduced after all doses, with a reduction continuing to 23h after doses of 10 mg and above.
- 3 The mean elimination half-life of SL 75212 was 17.5 ± 3.9 h. The plasma clearance ranged from 0.15 – 0.48 l kg⁻¹ h⁻¹ and the volume of distribution from 5.8 – 13 l kg⁻¹.
- 4 There was a significant correlation between the peak blood levels and change in exercise heart rate ($r=0.53$, $P<0.05$) and between the area under the blood concentration curve and the effect on the exercise heart rate ($r=0.55$, $P<0.01$).

Introduction

Although the number of β -adrenergic receptor blocking drugs in clinical use is large, a new member of this class, betaxolol (SL 75212), seemed to merit study in man because of its interesting pharmacological profile.

SL 75212 is ($\pm$)-1-(isopropylamino)-3[*p*-(2-cyclopropyl-methoxyethyl)-phenoxy]-2-propanol HCl with the molecular formula C₁₈ H₃₀ NO₃Cl, and a molecular weight of 348.89 (Manoury, personal communication).

SL 75212 has been shown to possess β -adrenoceptor-selectivity comparable to practolol in animal studies (Boudot, Caverio, Fénard, Lefevre-Bourg, Manoury & Roach, 1979).

There was no evidence of partial agonist activity and the local anaesthetic properties of the drug were very low.

β -adrenoceptor potency of SL 75212 was similar to that of propranolol by the intravenous route but three to thirty times higher by the oral route, depending on the experimental preparation.

Pharmacokinetic studies in dogs showed a low first-pass effect. The kinetic profile in conscious dogs was different from that of other 'cardioselective' β -adrenoceptor-blockers, in that it possessed good bioavailability, a high volume of distribution, a longer blood half-life, and reduced rate of elimination.

SL 75212 therefore appeared in the species tested to be a potent cardioselective compound without intrinsic sympathomimetic activity, with the possibility of consistent dose-related responses resulting from its low first-pass loss, and with a long duration of action. These properties suggested that it was worthwhile giving the compound to man. This paper reports the results of the first of these studies.

A pilot study was carried out to establish the short-term safety of the drug as well as a dose range. SL 75212 was administered to eight healthy males, all of whom gave informed consent, using an open technique, with constant electrocardiographic recording for 23h in the Coronary Care Unit of the General Hospital, Birmingham. Haematological and biochemical profiles and urine analysis were carried out before and after the study. Increasing doses from 1 mg to 40 mg were given, at intervals of at least two days.

The results indicated that the drug had significant cardiovascular effects and was without hazard in the short-term.

Methods

When the pilot study had shown the safety and efficacy of SL 75212, a further group was

Figure 1 Heart rate at rest (a) and during exercise (b). Mean ($n=6$) after SL 75212 5 mg ($\circ$ — $\cdots$ — $\circ$), 10 mg ($\blacktriangle$ — $- - -$ — $\blacktriangle$), 20 mg ($\bullet$ — $\bullet$ — $\bullet$), 40 mg ($\blacksquare$ — $\blacksquare$ — $\blacksquare$) or placebo ($\square$ — $- - -$ — $\square$).

investigated. This protocol and that of the pilot study were approved by the local Ethical Committee. The participants all gave informed consent.

Six healthy male volunteers age 21–40 years took part. They had no history of asthma, allergy, depression, renal or hepatic disease. All had a pulse rate greater than 50 beats/min and a normal E.C.G.

The following were established as being within normal limits before the study was entered: Hb, PCV, MCHC, RBC, ESR, platelets, WBC differential; routine liver and kidney function tests; urine analysis; antinuclear factor negative; Australia antigen negative. The E.C.G.s of subjects were followed on a monitor screen as well as on a recording trace for the whole study. The night following drug intake was spent in hospital.

No therapy of any kind was taken in the 48 h before each test. There was no smoking for 2 h before any heart rate or blood pressure measurements were made.

No alcohol was taken in the 24 h before each test. From midnight before each test, until its completion 23 h after taking the drugs, no beverage containing caffeine was taken. On the day of each test, a light breakfast of permitted beverages and lightly-buttered toast and preserves was taken at least 2 h before ingesting the drug. The breakfast was of the same type and quantity each day.

As part of the pre-study assessment of each subject

5 min periods of exercise on the bicycle ergometer were carried out with increasing workloads at half-hourly intervals until a load was found which produced a heart rate (measured from ten consecutive QRS complexes) of at least 140 beats/min during the last 20 s of exercise. This individually determined workload was used for that particular subject throughout the rest of the study (Åblad, Ervik, Haulgren, Johnsson & Sölvell, 1972).

Pulse was measured by calculation from the E.C.G. Blood pressure was measured manually with a mercury sphygmomanometer. All were determined before and in the last 20 s of the exercise periods. Peak expiratory flow rate was assessed with a Wright Peak Flow Meter immediately after the end of exercise.

Doses were given double-blind in a random manner. At each dose level two capsules were used to give doses of 0, 5, 10, 20, 40 mg to each subject. The capsules were swallowed with 100 ml of water. After the preliminary evaluation, each subject underwent five tests at weekly intervals. A final blood and urine check was carried out 1 week after the final dose.

Blood was collected into heparinized plastic tubes and stored at -20°C prior to analysis and urine collected 0–6, 6–12 and 12–24 h.

The subjects were asked to report any untoward effect or feeling at any time as it occurred.

Detailed procedure

Full resuscitation facilities were available, including intravenous isoprenaline. After resting supine for 30 min pulse, heart rate and E.C.G. were recorded. Peak expiratory flow rate was measured three times and 5 ml blood collected. Exercise was carried out for 5 min with measurement of PEFR every minute and pulse, blood pressure and E.C.G. during the last 20 s. The drug was ingested at 09.00 h and all resting and exercise measurements were repeated after 1, 2, 3, 4, 6, 8, 9, 10 and 23 h. Blood was collected at 1, 3, 6, 8, 23 and 24 h.

Determination of SL 75212

The drug was measured by a gas chromatographic method using a Perkin Elmer 3920 B gas-chromatograph equipped with an electron capture detector (Bianchetti, Ganansia & Morselli, 1979). The column was glass tubing (2 m $\times$ 3 mm i.d.) packed with 3% OV 17 on Chromosorb WAW-DMCS. The determination was based on an extraction of SL 75212 and its internal marker propranolol by diethyl ether from alkalized blood. After several steps of purification both compounds were derivatized with heptafluorobutyric anhydride to form a fluorinated derivative which could be measured with an electron capture detector.

The absolute sensitivity of the method was 1 ng/ml of blood and the standard curve was linear to a concentration greater than 100 ng/ml. The coefficient of variation ranged from $\pm 10\%$ for concentrations of 5–10 ng/ml to $\pm 5\text{--}8\%$ for levels of 15–85 ng/ml.

Statistical analysis

For each subject the parameter values have been expressed as percentages of the basal values.

For each parameter a multivariate analysis of variance (MANOVA) has been used to compare placebo and the four different doses considering simultaneously the values at each time.

A univariate analysis of variance (ANOVA) has been used to compare the drug effect at each time point.

The analyses have been done by using the SPSS statistical package (SPSS—Statistical Package for Social Sciences—version 6—Control Data Corporation and Northwest University, Minneapolis, 1977).

The area under the concentration curve, volume of distribution, half-life and total body clearance were calculated using standard methods (Gibaldi & Perrier, 1975).

Results

Heart rate

The mean resting heart rate is shown in Figure 1 a and that after exercise in Figure 1 b. The results show that all dose levels of SL 75212 significantly slowed the heart after exercise ($P < 0.05$) (Table 1). The effect was first apparent 2 h after giving the drug. At the 20 and 40 mg doses the relative bradycardia was still present at 23 h at which time the study was terminated. The effect of each dose at the various time points is shown in Figure 2. Within the dose

Figure 2 Exercise heart rate (mean $\pm$ s.e. mean, $n=6$) before and at intervals up to 23 h after single oral doses of SL 75212.

range studied, there appeared to be a maximal effect at 20 mg from 3 to 6 h but before 3 h and from 8 to 23 h there was greater activity with the 40 mg dose. Resting heart rate was less obviously affected, but nevertheless a change was noted with doses of 20 mg upwards ($P < 0.05$ at all times from 2 to 23 h).

Blood pressure

There was no significant change in diastolic blood pressure but systolic blood pressure at rest and after exercise was lowered by the drug (Table 2a, b).

Table 1 Heart rate during exercise after single oral doses of SL 75212 (mean $\pm$ s.e. mean, $n=6$)

Dose of SL 75212	0	1	2	3	Time(h) 4	6	8	10	24
Placebo	148.5 ± 9.64	146.0 ± 8.21	146.3 ± 8.22	147.7 ± 10.5	149.3 ± 10.1	149.3 ± 6.86	147.0 ± 7.37	153.7 ± 6.05	142.3 ± 11.09
5 mg	149.3 ± 5.53	140.3 ± 7.09	130.3** ± 7.63	122.7*** ± 5.72	127.2*** ± 5.46	128.7** ± 5.31	130.0*** ± 4.10	132.5*** ± 4.59	137.8 ± 5.11
10 mg	146.0 ± 7.47	132.3 ± 3.74	126.7*** ± 4.49	123.0*** ± 5.21	122.7*** ± 5.05	126.0** ± 5.41	126.7*** ± 5.95	130.0*** ± 6.32	133.2 ± 6.80
20 mg	147.0 ± 6.02	122.3 ± 7.01	117.0†† ± 3.61	114.0† ± 4.41	114.0† ± 4.59	115.7† ± 5.78	117.3† ± 5.58	120.7† ± 5.95	124.3† ± 5.35
40 mg	147.0 ± 5.21	135.7 ± 6.78	113.7†† ± 2.80	111.3† ± 3.25	113.3† ± 3.68	114.3† ± 3.32	113.5† ± 2.75	117.0† ± 3.30	118.7† ± 4.28

Significant difference from placebo values: ** < 0.01 ; *** < 0.001

Significant difference from values after 10 mg: † < 0.05 ; †† < 0.01

Figure 3 Blood concentrations of SL 75212 in six volunteers after four different doses given orally (○ 5 mg, △ 10 mg, ● 20 mg and ■ 40 mg).

Resting systolic blood pressures were significantly reduced at +3 h by all dose levels of SL 75212. At +8 h the difference was only significant for the 20 and 40 mg doses ($P < 0.01$).

Systolic pressure after exercise was significantly reduced by all dose levels of SL 75212 ($P < 0.05$). The effect could not be shown beyond 8 h for the 5 mg dose but was still significant at 23 h for the other doses (placebo > 5, 10, 20, 40 mg, $P < 0.01$ from 1 to 6 h, $P < 0.05$ at 8 h; placebo and 5 mg > 10, 20, 40 mg, $P < 0.05$ at 10 h, $P < 0.01$ at 23 h).

Peak expiratory flow rate

No statistical difference between SL 75212 and placebo could be shown either before or after exercise when PEFR was measured.

Pharmacokinetics

Blood concentration The individual concentrations obtained for each subject are plotted in Figure 3. Peak blood concentrations ranged between 8–14, 14–28, 32.5–60.5 and 51.5–119 ng/ml for the 5, 10, 20 and 40 mg doses respectively.

Pharmacokinetic analysis The half-life, volume of distribution, area under the curve and plasma clearance values were calculated assuming 100%

bioavailability. In Table 3 the means of the values obtained for the four different doses are presented for each subject (individual results at each dose for the AUC) and in Table 4 the means of the values obtained for the six subjects are presented for each dose.

In general the apparent plasma half-life (T_1) lay between 13 and 21 h although there were one or two cases in which the values were larger. There was approximately a twofold variation in the values obtained for plasma clearance and for volume of distribution, for which the values were 0.15–0.48 l $\text{kg}^{-1} \text{h}^{-1}$ and 5.8–13 l kg^{-1} respectively.

It is apparent from Table 4 that the intersubject variation is very small and the half-life, volume of distribution and plasma clearance rate are independent of dose over the range of 5–40 mg.

$\text{AUC}_{0-\infty}$ have been calculated for each dose in each subject and significant linear relationship has been found between doses and $\text{AUC}_{0-\infty}$ values. There is a good agreement between the dose and $\text{AUC}_{0-\infty}$ as can be seen from Table 4.

Urinary excretion of unchanged SL 75212 For four of the subjects the 24 h urinary recovery at all dose levels was between 3.5 and 8.2%. For Subject 6 recoveries were higher, with 13.3 and 14.3% recovered on two occasions. The percentage recovered in the urine of Subject 3 was never less than 16% and after the 5 mg dose was almost 40%. Subsequent experience has shown this to be an anomalous finding. Both the peak blood concentration and AUC after the 5 mg dose in Subject 3 were considerably higher than the values obtained in the other subjects.

Relationship of pharmacokinetic data to pharmacodynamics There was a significant correlation ($r = 0.53$, $P < 0.05$) between peak blood levels of SL 75212 and change in heart rate on exercise. There was also a significant correlation between the AUC_{0-23} and AUC_{0-23} of effect on post-exercise heart rate ($r = 0.55$, $P < 0.01$).

Side-effects

There were no side-effects reported or observed apart from one episode of diarrhoea and vomiting that developed 6 h before drug intake and lasted for 12 h after the 10 mg dose in one subject.

Discussion

These results show that SL 75212 is an effective and long lasting β -adrenoceptor blocking agent in man.

In single doses up to 40 mg there were no side effects. Although no effect on the peak expiratory flow rate could be demonstrated, the design of the study did not include a positive control.

Table 2a Systolic blood pressure (mmHg) at rest after single oral doses of SL 75212 (mean $\pm$ s.e. mean, $n=6$)

Dose of SL 75212	0	1	2	3	Time (h) 4	6	8	10	24
Placebo	112.0 ± 7.47	109.5 ± 4.33	109.3 ± 2.11	113.5 ± 4.54	115.3 ± 5.58	109.3 ± 7.83	111.8 ± 3.0	115.2 ± 2.59	117.2 ± 4.68
5 mg	116.7 ± 3.72	110.5 ± 5.08	108.8 ± 2.71	106.7* ± 4.61	104.2 ± 3.75	99.0 ± 3.65	110.0 ± 2.89	107.3 ± 2.40	111.0** ± 4.09
10 mg	118.0 ± 5.77	112.5 ± 5.69	110.8 ± 6.9	107.2* ± 4.31	105.8 ± 4.5	105.8 ± 4.5	112.8 ± 5.89	114.2 ± 5.83	106.0** ± 3.41
20 mg	117.7 ± 4.57	105.8 ± 3.43	106.7 ± 3.04	103.8* ± 6.43	104.3 ± 3.28	108.0 ± 3.04	102.0** ± 3.61	106.7 ± 3.33	109.7** ± 4.66
40 mg	119.5 ± 3.93	116.3 ± 6.93	104.3 ± 4.48	103.7* ± 2.39	104.8 ± 3.75	103.7 ± 1.28	102.0** ± 3.3	104.3 ± 3.67	102.7** ± 4.05

Significant difference from placebo values: * < 0.005 ; ** < 0.01 **2b** Systolic blood pressure (mmHg) during exercise after single oral doses of SL 75212 (mean $\pm$ s.e. mean, $n = 6$)

Dose of SL 75212	0	1	2	3	Time (h) 4	6	8	10	24
Placebo	140.7 ± 7.77	140.7 ± 5.99	133.3 ± 8.82	135.5 ± 7.89	134.3 ± 10.01	140.5 ± 6.18	141.3 ± 5.45	143.3 ± 3.33	146.0 ± 5.77
5 mg	147.2 ± 6.06	139.8 ± 6.38	138.0** ± 5.32	132.5 ± 2.83	133.7** ± 5.04	126.7** ± 3.33	135.2* ± 4.83	136.7 ± 6.15	151.7 ± 2.99
10 mg	151.2 ± 5.01	137.8 ± 8.42	132.0** ± 5.59	126.0** ± 3.14	135.7** ± 2.28	128.3** ± 3.07	137.2* ± 4.00	135.8* ± 4.55	139.6** ± 3.60
20 mg	152.2 ± 4.48	127.0** ± 7.43	127.3** ± 3.63	125.7** ± 2.85	125.8** ± 4.55	127.5** ± 3.59	126.7* ± 5.05	129.3* ± 4.94	131.5** ± 3.70
40 mg	150.0 ± 6.83	133.7** ± 8.75	121.0** ± 5.63	120.2** ± 3.47	120.3** ± 3.71	123.8** ± 4.61	116.7* ± 3.07	119.7* ± 0.33	127.0** ± 3.99

Significant difference from placebo values: * < 0.05 ; ** < 0.01 **Table 3** Half-life ($T_{1/2}$) and volume of distribution (V_d), apparent clearance (Cl) and area under the curve ($AUC_{0-\infty}$) of SL 75212 at each dose level (mean $\pm$ s.e. mean, $n = 6$)

Dose (mg)	$T_{1/2}$ (h)	V_d ($l\ kg^{-1}$)	Cl ($l\ kg^{-1}\ h^{-1}$)	$AUC_{0-\infty}$ ($ng\ ml^{-1}\ h$)
5	19.0 $\pm$ 2.2	7.5 $\pm$ 0.09	0.30 $\pm$ 0.03	279.2 $\pm$ 33.6
10	19.5 $\pm$ 5.1	7.5 $\pm$ 0.7	0.32 $\pm$ 0.06	545.8 $\pm$ 107.7
20	17.0 $\pm$ 2.8	7.5 $\pm$ 0.7	0.32 $\pm$ 0.02	992.5 $\pm$ 72.2
40	17.2 $\pm$ 2.0	9.0 $\pm$ 1.0	0.37 $\pm$ 0.03	1 782.5 $\pm$ 213.2

Table 4 Half-life ($T_{1/2}$) and volume of distribution (V_d) and apparent clearance (Cl) of SL 75212 in each subject calculated as a mean $\pm$ s.e. mean of the values obtained after four different doses

Subject	$T_{1/2}$ (h)	V_d ($l\ kg^{-1}$)	Cl ($l\ kg^{-1}\ h^{-1}$)
1	21.0 $\pm$ 6.0	8.4 $\pm$ 0.9	0.32 $\pm$ 0.06
2	15.4 $\pm$ 1.3	7.9 $\pm$ 0.8	0.35 $\pm$ 0.02
3	14.4 $\pm$ 2.4	7.0 $\pm$ 0.4	0.35 $\pm$ 0.04
4	19.2 $\pm$ 2.9	7.0 $\pm$ 0.4	0.26 $\pm$ 0.02
5	19.0 $\pm$ 2.9	8.9 $\pm$ 0.4	0.36 $\pm$ 0.06
6	17.9 $\pm$ 3.0	8.3 $\pm$ 1.5	0.32 $\pm$ 0.02

The relatively wide scatter of two to five times in the interindividual plasma levels of atenolol 2 h after oral administration (Shanks, Carruthers, Kelly & McDevitt, 1975) would be in keeping with incomplete and variable absorption. Wan, Koda & Maronde (1979) found that atenolol bioavailability was only 50% after oral administration. The poor reproducibility of propranolol blood levels is due to a high first-pass loss (Routledge & Shand, 1979). In contrast the small intersubject variability in blood levels in the present study with SL 75212 suggests that absorption is good and presystemic hepatic ('first-pass') elimination of this compound may be low. This hypothesis is supported by the close correlation of the dose administered and the area under the blood concentration curve. In this respect, SL 75212 resembles practolol (Carruthers, Ghosal, McDevitt, Nelson & Shanks, 1974), rather than alprenolol (Åblad *et al.*, 1972), oxprenolol (Riess, Rajagopalan, Imhof, Schmidt & Keberle, 1970), or metoprolol (Johnsson, Regardh & Sölvell, 1975). Although the non-selective β -adrenoceptor blocker nadolol, which has been recently introduced into clinical practice, undergoes little first-pass loss, absorption from the gastrointestinal tract of man is incomplete and variable, single doses being only 20.4–33.3% absorbed (Dreyfuss, Shaw & Ross, 1978). This resulted in the need for relatively high doses (up to 560 mg/day, mean 11 mg/day) in the treatment of essential hypertension (Frithz, 1978).

The elimination half-life of SL 75212 (mean 17.5 ± 3.9 h) appears to be longer than that of other β -adrenoceptor-blockers, e.g. propranolol 2–4 h after single doses (Shand, 1974) and 4–6 h after repeated

administration (Evans & Shand, 1973), practolol 11 h (Carruthers, Kelly, McDevitt & Shanks, 1974), pindolol 2.9 h (Jennings, Bobik, Fagan & Korner, 1979), atenolol 6 h (McAinsh, 1977), metoprolol 4–6 h (Johnsson *et al.*, 1975) and nadolol 12.2 h oral and 9.9 h intravenous (Dreyfuss, Brannick, Yukovich, Shaw & Willard, 1977). Watson & Littler (1979) found that 24 h after the fifth daily dose of 400 mg acebutolol, reduction in exercise heart rate was only 5%, compared to 25% at the time of peak activity.

The blood levels used for calculation of the elimination half-life of SL 75212 were measured by a specific gas-liquid chromatography method (Bianchetti *et al.*, 1979). Although the metabolism of the molecule remains to be fully elucidated, it is thought that pharmacologically active metabolites are not produced from SL 75212 (Dring, personal communication). The long duration of action which produces significant β -adrenoceptor-blockade for at least 23 h after a single 10 mg dose is due to persistence of the parent compound. The low urinary recovery of unchanged SL 75212 and the slow elimination of metabolites has now been confirmed by a study using ^{14}C -labelled SL 75212 (Sever, personal communication).

Further studies are required to elucidate the degree of cardioselectivity in man as well as the tolerance and pharmacokinetics after repeated administration, and the measurement of the absolute bioavailability by direct comparison of the pharmacokinetics after oral and intravenous administration. These first results in man suggest that, by its long duration of action and narrow dose range SL 75212 may prove to be a clinically useful β -adrenoceptor blocking agent.

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