Pharmacokinetic and pharmacodynamic comparison of two doses of long acting propranolol (80 and 160 mg) in healthy subjects

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- 1 The kinetics and dynamics of long acting propranolol 80 mg and 160 mg were examined after single oral doses to 12 healthy volunteers.
- 2 Long acting propranolol 160 mg produced a twofold increase in mean peak blood propranolol concentration and AUC compared with the lower dose. There was no difference in elimination half-life, bioavailability and mean residence time of propranolol between the two doses.
- 3 Resting pulse rate was decreased by long acting propranolol 160 mg but not by the lower dose.
- 4 Both preparations blocked exercise induced tachycardia during the entire observation period of 29 h. Percentage inhibition of exercise tachycardia was significant at all time points but long acting propranolol 160 mg exhibited a greater reduction at 24 h and 29 h.
- 5 Increase in systolic blood pressure during exercise was inhibited by both preparations during the entire observation period with no differences between them.
- 6 The doubling of the dose administered was reflected in blood concentrations but not in pharmacodynamic parameters. Few pharmacodynamic differences were found between the two doses.

Keywords long acting propranolol 80 and 160 mg pharmacokinetics pharmacodynamics

Introduction

β -adrenoceptor blocking drugs are among the most frequently prescribed classes of drugs. However since the half-life of many β -adrenoceptor blockers is relatively short multiple daily dosing is required to maintain a therapeutic effect throughout the day. This repeated daily dosing may diminish patient compliance and therefore the efficacy of the treatment.

A long acting formulation of propranolol (Inderal LA) has been used to maintain thera-

peutic plasma propranolol concentrations throughout the day following once daily administration. The systemic bioavailability was between 50 and 80% of that for conventional propranolol (McAinsh *et al.*, 1978; Leahey *et al.*, 1980; Serlin *et al.*, 1983). The apparent elimination half-life of long acting propranolol is approximately two to three times that of conventional propranolol (Leahey *et al.*, 1980). Furthermore the long-acting formulation results

in lower peak concentrations, but a longer duration of action (McAinsh *et al.*, 1978; Leahey *et al.*, 1980).

Thus, a single daily dose of long acting propranolol 160 mg produces significant β -adrenoceptor blockade throughout a 24 h period, but the question arises as to whether a lower dose would be sufficient to produce significant β -adrenoceptor blockade over 24 h.

Methods

Subjects

Twelve healthy male volunteers were selected for the study. Their ages ranged from 20 to 34 years (mean 26.5), their weight from 58 to 85 kg (mean 68 kg) and height from 167 to 189 cm (mean 178 cm). Every subject had normal results following clinical, biochemical and haematological examinations before the study. In addition they had normal 12 lead ECGs. Approval was obtained from the appropriate Ethics Committee and each subject gave written informed consent before the study. Subjects were asked not to drink alcohol and caffeine containing beverages on study days and during the 24 h prior to study days. They did not take any other medication during the 8 days preceding the trial.

Drug supply and experimental design

A single-blind cross over procedure was used. Capsules of the long-acting formulation containing 80 mg or 160 mg propranolol hydrochloride were supplied by I.C.I. Pharma (Avlocardyl LA 80 and 160 mg). Each subject was dosed in a randomized order either one capsule of long acting propranolol 80 mg (LA propranolol 80) or one capsule of long acting propranolol 160 mg (LA propranolol 160). Drug administration was separated by a period of 8 days during which subjects did not take any medication.

Study procedures

At the pre-study investigation a bicycle ergometer exercise test was performed in order to verify whether subjects were able to maintain a workload of 120 W for 3 min without presenting clinical signs and/or physical intolerance.

During the trial, subjects spent each study day in the laboratory from 07.00 h to 13.00 h the following day. During this period exercise tests were performed before, 4, 24, and 29 h after the administration of the treatments.

For the exercise test a bicycle ergometer with electromagnetic braking (Corival 300) was used. The initial load of 30 W was increased by 30 W every 3 min (30, 60, 90 and 120 W). ECG was recorded continuously from precordial leads. Pulse rate, systolic and diastolic blood pressure were measured before the exercise test in the sitting position and after each exercise level. Resting pulse rate was also recorded before each venesection throughout the day.

Blood was drawn for the determination of blood propranolol concentration before and 1.5, 3, 4, 5, 6, 9, 12, 15, 24 and 29 h after drug administration.

Blood propranolol levels were determined by high pressure liquid chromatography using metoprolol as internal standard (Rosseel *et al.*, 1982) with fluorescence detection at 220nm (excitation) and 300nm (emission). The variation coefficient of the method varies from 4% (for blood propranolol level of about 2.5 ng ml⁻¹) to 2.5% (for blood propranolol level of about 20 ng ml⁻¹). The lower limit of the detection is 0.2 ng ml⁻¹.

Data analysis

Pharmacokinetic data were analysed as follows:

The mean $C_{\max}$ and $t_{\max}$ were calculated from the individual peak blood propranolol concentrations.

The area under the blood concentration-time curve was determined by trapezoidal rule until the last concentration measured (AUC_p) and extrapolated to infinity using the equation $AUC = AUC_p + C_t/ke$ where C_t represents the last blood concentration measured. ke is the apparent elimination rate constant obtained by linear regression of the log blood concentration against time of the terminal phase. The apparent elimination half-life was calculated using the equation $t_{1/2} = 0.693/ke$.

In order to take into account the intrasubject variability of the $t_{1/2}$ calculations the apparent volume of distribution was assumed to be constant in each volunteer administered either treatment. The correction proposed by Koup & Gibaldi (1980): $FD/V_d = AUC \cdot ke$ was then used to calculate the apparent bioavailability corrected by V_d using the equation: $F/V_d = AUC \cdot ke/D$, then allowing a better approach to the estimation of bioavailability.

The mean residence time was calculated using the equation: $MRT = AUMC/AUC$, where AUMC is the AUC of the product of time and blood concentration (area under the first moment of the blood concentration-time curve).

The ratio of these two values, calculated for

each dose, represents the relative bioavailability of the 80 mg dose relative to that of the 160 mg dose.

Statistical analysis

Pharmacodynamic parameters were tested by analysis of variance with three between subject factors (subject, occasions and drugs) and two within subject factors (times and workload).

Pharmacokinetic data were analysed as follows. Wilcoxon's rank test was used for comparison of $t_{\max}$. Blood propranolol concentrations were compared at each time point by Student's paired t -test. For the variables $C_{\max}$, AUC_p, AUC and MRT three-way ANOVA taking into account subject, order of treatment and drugs was applied. The relationship between blood propranolol concentration (log-transformed) and effect was examined by least square regression analysis. Results are expressed as mean $\pm$ s.d. A P value 0.05 was considered to be significant.

Results

Pharmacokinetics

Figure 1 shows mean blood propranolol concentrations and Table 1 summarizes the pharmacokinetic parameters.

Mean blood propranolol concentrations were significantly different at each time point except 1.5 h (Figure 1).

Mean maximal blood propranolol concentration was significantly different between the two formulations but the time required to reach maximal blood concentration ($t_{\max}$) was not. There was no difference in the mean apparent elimination half-life and in the time during which blood propranolol concentrations were higher than the half of the maximal blood concentrations ($C_{\max}/2$).

The mean AUC calculated from 0 to 29 h (AUC_p) and the mean AUC extrapolated to infinity (AUC _{∞}) were significantly different ($P < 0.001$). On normalising these values for the dose administered, the difference became non-significant. The comparative bioavailability of LA propranolol 80 vs 160 was 1.17. The MRT was the same after the two treatments.

Pharmacodynamics

Resting pulse rate was significantly reduced by LA propranolol 160 ($F = 3.08$, $P = 0.039$) but not by LA propranolol 80 ($F = 2.25$, $P = 0.099$).

Figure 2 illustrates the pulse rate during exercise test as a function of the workload. There was no difference between the two formulations in exercise tachycardia ($F = 1.23$, NS). A significant time effect ($F = 29.3$, $P < 0.001$) and a significant effect of workload ($F =$

Figure 1 Mean (s.e. mean) blood propranolol concentrations observed after oral administration of long acting propranolol 80 mg (●) and 160 mg (□). * $P < 0.005$, ** $P < 0.001$.

Table 1 Pharmacokinetic parameters calculated after oral administration of a single dose of long acting propranolol 80 and 160 mg to healthy subjects. Values are mean ($\pm$ s.d.)

	80 mg	Propranolol 160 mg	P
$t_{\max}$ (h)	5.3 (1.7)	4.9 (1.9)	NS
$C_{\max}$ (ng ml ⁻¹)	6.9 (3.6)	13 (7.2)	<0.001
$t_{1/2}$ (h)	21.8 (13.6)	22.9 (16.3)	NS
AUCp (ng ml ⁻¹ h)	114.2 (68.6)	201.4 (118.3)	<0.001
$C_{\max}/2$ (h)	16.99 (5.71)	16.33 (6.01)	NS
AUC (ng ml ⁻¹ h)	211.8 (149.3)	411.1 (467.6)	<0.001
FD/Vd (ng l ⁻¹)	7.12 (3.86)	12.09 (6.98)	<0.001
MRT (h)	12.6 (1.1)	12.8 (0.9)	NS

Figure 2 Exercise induced tachycardia as a function of workload before (0 h) and 4, 24 and 29 h after single administration of 80 mg (●) and 160 mg (□) of long acting propranolol.

292.3, $P < 0.001$) could be seen for both treatments. No significant time $\times$ dose interaction was observed. However a significant interaction between workload and doses was found ($F = 7.37$, $P < 0.001$). Both treatments blocked exercise tachycardia at every time point at every level of workload.

Resting systolic blood pressure was lowered by both treatments ($F = 3.85$, $P < 0.02$ for LA propranolol 80 and $F = 8.18$, $P < 0.001$ for LA propranolol 160) but there was no significant difference between them.

The increase in systolic blood pressure during exercise (Figure 3) was significantly obtunded by both treatments ($F = 176.2$, $P < 0.001$) but there was no difference between them ($F = 1.88$, NS).

Both drug formulations exhibited a significant time effect ($F = 13.0$, $P < 0.001$) on the systolic blood pressure increase during exercise. LA propranolol 160 obtunded systolic blood pressure increase at every level of workload at every point of time. LA propranolol 80 did the same except at the 120 W workload: at which point there was no significant effect over time ($F = 2.35$, NS). Thus the systolic blood pressure increase escaped. There was no modification in diastolic blood pressure.

Percentage inhibition of exercise tachycardia is shown on Figure 4. The mean baseline (pre-drug) exercise tachycardia at 120 W was 140 ± 13.3 beats min⁻¹ before LA propranolol 80 and 141 ± 11 beats min⁻¹ before LA propranolol

Figure 3 Mean systolic blood pressure during exercise test before (0 h) and 4, 24 and 29 h after single administration of 80 mg (●) and 160 (□) of long acting propranolol.

Figure 4 Blood propranolol concentration and inhibition of exercise tachycardia 4, 24 and 29 h after single administration of 80 mg (●) and 160 mg (□) of long acting propranolol (mean $\pm$ s.e. mean). * $P < 0.05$, ** $P < 0.02$, *** $P < 0.005$.

160. Maximal inhibition of exercise tachycardia was reached at 4 h for both treatments ($11.5 \pm 4.3\%$ for LA propranolol 80 and $13.4 \pm 6.1\%$ for LA propranolol 160, NS). At 24 h the decrease in exercise tachycardia was $8.6 \pm 5.4\%$ after LA propranolol 80 and $12.5 \pm 5.2\%$ after LA propranolol 160 ($P < 0.05$). Both drug formulations obtunded exercise tachycardia significantly at 29 h (LA propranolol 80: 6.9 ± 6.4 , $P < 0.01$; LA propranolol 160: 11.9 ± 5.5 , $P < 0.001$) but there was a difference in the degree of β -adrenoceptor blockade. The effect of LA propranolol 160 on exercise tachycardia was more intense at 29 h ($P < 0.02$). No correlation was found between the percentage inhibition of exercise tachycardia and blood propranolol log-concentration for LA propranolol 80 ($r = 0.26$, NS) but a significant correlation was found for LA propranolol 160 ($r = 0.56$, $P = 0.0003$).

Discussion

In this study we compared the pharmacokinetic and pharmacodynamic properties of two doses of a long-acting propranolol preparation. We found that LA propranolol 160 mg produced a twofold rise in peak blood propranolol level and AUC relation to the lower dose but doubling the dose did not influence the elimination half-life, bioavailability and mean residence time of the drug. Despite the two-fold increase of blood propranolol concentration, pharmacodynamic

activity of the two long acting propranolol preparations showed no significant differences.

The absorption of propranolol was not altered by the dose administered: the $t_{\max}$ s were identical (median 5.5 h) for both formulations and the blood concentration profiles were superimposable as determined by the time during which concentrations were higher than $C_{\max}/2$ (17 ± 5.7 h for LA propranolol 80 and 16.3 ± 6 h for LA propranolol 160). Maximal propranolol concentrations were proportional to the dose but a wide interindividual variability (from 1 to 7 for $C_{\max}$) was observed as already shown by Routledge & Shand (1979) with conventional propranolol preparations.

After oral administration the bioavailability of conventional propranolol formulations is reduced because of the important pre-systemic metabolism of the drug. The bioavailability of the long acting propranolol has been estimated to be 50–80% (McAinsh *et al.*, 1978), 50% (Serlin *et al.*, 1983) and 68% (Leahey *et al.*, 1980), that of the conventional tablet. The lack of a relationship between the propranolol dose and its blood (or plasma) concentrations and consequently its lack of a relation between the dose and the bioavailability has been observed in many studies (Walle *et al.*, 1978; Dey *et al.*, 1986; Kopitar *et al.*, 1986). These studies used doses ranging from 10 to 160 mg following single or repeated administration of conventional propranolol. Wagner (1985) outlined that the bioavailability of propranolol is closely correlated with the rate of administration. In steady state the mean plasma propranolol concentration has a direct relation with the Michaelis-Menten (K_m , $V_{\max}$) constant. Thus, the higher the number of dosing intervals the more the bioavailability decreases. Consequently, long acting preparations will have a smaller bioavailability than conventional propranolol formulations as observed previously.

In the present study the bioavailability did not differ between the two doses and this has been observed previously (Dvornik *et al.*, 1983).

In our study the mean apparent elimination half-life of propranolol was longer than that published by McAinsh *et al.* (1978, 1981). The lengthening of the elimination half-life may be the result of overestimating this parameter. In our study blood sampling was interrupted at 29 h whereas in the studies of McAinsh it was continued until the 48th hour. As absorption took over the elimination, the value of half-life increased and led to an imprecision in the calculation of elimination half-life. This required us to use the correction recommended by Koup & Gibaldi (1980).

There were few differences in pharmacodynamic activity between the two LA propranolol formulations. Both treatments exhibited a prolonged β -adrenoceptor blockade as has already been shown by Wautrecht *et al.* (1982) in a placebo controlled study with Inderal LA. In our study in spite of the doubling of the dose and the proportional increase in blood propranolol levels the differences in exercise induced tachycardia and blood pressure increase were moderate. Differences between the two doses of LA propranolol were seen only in percentage reduction of exercise tachycardia at 24 and 29 h after drug administration but no differences occurred in exercise tachycardia taking the absolute values of pulse rate. The increase in systolic blood pressure was blocked by the treatments throughout the day, the only difference appeared at 29 h after administration when at the highest workload level systolic blood pressure escaped β -adrenoceptor blockade after LA propranolol 80 but not after LA propranolol 160. On the other hand, resting pulse rate was significantly decreased by LA propranolol 160 but not by LA propranolol 80.

Many studies have demonstrated correlations between plasma (or blood) levels of propranolol and its pharmacological effect (Coltart & Shand, 1970; Pine *et al.*, 1975; McAinsh *et al.*, 1978; Mullane *et al.*, 1982) but others could not establish this correlation (Krediet *et al.*, 1980; Lehtonen *et al.*, 1977).

Although we find a significant correlation between the logarithm of the blood propranolol levels and the percentage inhibition of exercise tachycardia for the 160 mg dose, the pharmacological effect did not follow the pharmacokinetic differences.

This disparity between blood propranolol concentration and pharmacological effect may result from the fact that the blood concentration with LA propranolol 80 was sufficient to obtain β -adrenoceptor blockade. Plasma (or blood) propranolol concentrations considered to be active are in fact very low. Pine *et al.* (1975) have shown that the concentration producing half of the maximum effect (EC_{50}) evaluated by inhibition of exercise tachycardia corresponded to 8 ng ml^{-1} in healthy volunteers. Esler *et al.* (1977) have estimated that the fall in blood pressure in patients with hypertension was significant with concentrations ranging from 3 to 30 ng ml^{-1} . Mullane *et al.* (1982) have observed that with plasma concentrations between 0.5 and 5 ng ml^{-1} 60% of subjects treated with propranolol had significant β -adrenoceptor blockade. The half-life of the pharmacological effect of conventional propranolol has been estimated to be 20 h

measured at rest and 14 h evaluated by exercise test while the chemical elimination half-life is only 3–8 h (Wellstein *et al.*, 1985). Furthermore 50% inhibition of the exercise tachycardia can be obtained with concentrations from 7 to 40 ng ml⁻¹. Thus, low plasma (or blood) propranolol concentrations seem to be sufficient to exhibit clinically relevant β -adrenoceptor blockade. This may be explained by taking the density of the β -adrenergic receptors into account (Tawara *et al.*, 1987). An incomplete saturation of the β -adrenoceptors may by sufficient to lead

to a pharmacological effect.

It may be concluded from our study that blood propranolol concentrations after LA propranolol 80 mg were sufficient to induce significant β -adrenoceptor blockade. Administration of LA propranolol 160 mg has no significant advantage over LA propranolol 80 mg.

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