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Comparative Pharmacokinetics and Pharmacodynamics of Propranolol and Atenolol in Normolipaemic and Hyperlipidaemic Obese Subjects

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ABSTRACT: The lipophilic beta-adrenoreceptor antagonist propranolol and hydrophilic atenolol have been studied to define their pharmacokinetic and pharmacodynamic characteristics in obese patients. A total of 43 subjects were allocated into three study groups: (1) healthy, lean, normolipaemic volunteers, (2) obese normolipaemic subjects, and (3) obese patients with lipid disorders. A crossover method with an interval of 2 weeks was applied for oral 80 mg propranolol and oral 100 mg atenolol administration. Heart rate as well as systolic and diastolic blood pressure were recorded during 24 h. At each time-point of measurement blood serum concentration of propranolol and atenolol were evaluated. Pharmacokinetic parameters of the drugs were calculated using a one-compartment open model for extravascular administration. There were no statistically significant differences in blood serum concentrations of propranolol between the studied groups. The concentrations of atenolol were significantly lower in both normolipaemic and hyperlipidaemic obese subjects. A trend towards increase in Vd/F and Cl/F of propranolol in obese patients with hyperlipidaemia were noted. In the case of water-soluble atenolol, the AUC, C_{max}, $Cl/(F \times BW)$ were significantly lower in obese hyperlipidaemic and normolipaemic patients in comparison with lean subjects. The pharmacodynamic effects of propranolol and atenolol in obese and lean subjects were of similar magnitude. The observed differences between obese and non-obese persons were clinically not relevant. Copyright © 2003 John Wiley & Sons, Ltd.

Key words: propranolol; atenolol; pharmacokinetics; pharmacodynamics; obesity; hyperlipidaemia

Introduction

Obesity, defined as a body mass index (BMI) of more than $30\,kg/m^2$ constitutes an increasing problem in most nations. Drug therapy in obese subjects is common in clinical practice, since obesity can be associated with many disease states requiring long-term drug administration such as diabetes, hypertension and cardiovascular disease [1]. Thus, efforts to optimize drug therapy in the obese provide a challenge to the clinician. Potential pharmacokinetic alterations seen in primary obesity may include changes in drug distribution, biotransformation and excretion. Drug distribution may differ from normal non-obese subjects due to marked changes in body composition documented in the obese population [2]. A reduced proportion of body water and muscle mass to total body weight, and a greater proportion of body fat may result in distributional changes among body compartments [3]. Drug biotransformation may also be altered in the obese population as a result of a high

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incidence of liver abnormalities and changes in hepatic blood flow [4, 5]. Further, the renal excretion of drugs may be modified in obese subjects due to changes in the renal blood flow and the glomerular filtration rate secondary to increased blood volume and cardiac output. Finally, lipid disorders frequently seen in obese subjects could influence the pharmacokinetics of drugs, as has been reported in previous studies [6–8].

The ß-blockers are of great therapeutic value in the treatment of cardiovascular diseases such as hypertension, coronary heart disease and arrhythmias, i.e. states often associated with obesity. The pharmacokinetics of ß-blockers depends on their lipid solubility. Lipophilic drugs, such as propranolol are extensively metabolized by the liver while hydrophilic ß-blockers, among them atenolol are predominantly excreted by the kidney. The variability in lipophilicity could further influence their pharmacokinetics and consequent haemodynamic effects of those drugs in obese patients [9, 10]. In the relatively few studies on the kinetics of ß-blockers in obese patients the authors did not investigate concomitant lipid disorders [11–13]. Our previous data suggested that lipid status could influence both the pharmacokinetics and pharmacodynamics of propranolol in hyperlipidaemia [7, 14]. In order to extend the previous studies it was decided to compare the pharmacokinetics and haemodynamic properties of lipophilic propranolol and hydrophilic atenolol in obese subjects with and without primary hyperlipidaemia.

Materials and Methods

Patients

The study was carried out in 43 nonsmokers divided into three study groups. The first group consisted of 18 subjects (13 men, 5 women) with a normal body weight (BMI 18.7–26.4 kg/m^2; mean $24.0 \pm 0.6\,kg/m^2$), aged 24–55 years (mean 43.2 ± 2.4 years). The second group included 9 patients (4 men, 5 women) with BMI 31.0–40.6 kg/m^2 (mean $35.6 \pm 1.2\,kg/m^2$), mean cholesterol level 188.2 ± 3.2 mg/dl, mean triglyceride level 114.4 ± 36.0 mg/dl, aged 25–55 years (mean 45.7 ± 3.3 years). The third group consisted of 16 (11 men, 5 women) obese patients (BMI 31.1–42.0 kg/m^2, mean $35.6 \pm 1.5\,kg/m^2$) with hyperlipidaemia (mean cholesterol level 297.8 ± 19.5 mg/dl, mean triglyceride level 431.0 ± 47.6 mg/dl), aged 32–55 years (mean 45.8 ± 3.5 years). The diagnosis of lipid metabolism disturbances was established on the basis of threefold measurement of blood triglycerides and total cholesterol in a fasting state, each measurement being taken with a 7 day interval. During the study period, all subjects remained on a hypolipaemic diet and were free of any medication for at least 2 weeks prior to the study (including oral contraceptives). All subjects had normal cardiac, respiratory, hepatic and renal function. All cases of secondary hyperlipidaemia were excluded from the study. The weight of all subjects had been stable for at least 2 months prior to the study period. The study protocol was approved by the Ethics Committee of Pomeranian Academy of Medicine, Szczecin, Poland, and was fully explained to all patients.

Pharmacokinetic studies

Subjects fasted overnight prior to oral administration of propranolol 80 mg (Polfa, Poland) or atenolol 100 mg (Polpharma, Poland). Ingested tablets were followed by 200 ml tap water. A light meal was permitted 3 h after the drug administration, and meals were permitted thereafter in the routine schedule. Blood samples of 5 ml were obtained from an indwelling catheter in the forearm vein before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after the morning drug administration. Propranolol and atenolol were administered in a crossover method with an interval of 2 weeks. Individual concentration versus time plots were calculated for each subject and the following pharmacokinetic parameters, based on the one-compartment open model for extravascular administration, were considered. The mean maximal plasma concentration (C_{max}) and time required to reach C_{max} (t_{max}) were calculated from the individual peak blood propranolol concentrations. The area under the plasma concentration-time curve (*AUC*) was determined by trapezoidal rule until the last concentration

measured and extrapolated to infinity. The terminal slope (λ_z) was obtained by linear regression of the terminal log plasma concentration data against time (4 to 6 points were used for regression). The elimination half-life ($t_{1/2}$) was calculated using the equation $t_{1/2}=\ln 2/\lambda_z$. The relative total body clearance ($Cl/(F \times BW)$, where BW-body weight, was calculated by equation: $Cl/(F \times BW)=\text{Dose}/(AUC \times BW)$. The relative apparent volume of distribution $V_d/(F \times BW)$ was calculated as the volume based on the terminal slope according to the equation: $V_d/(F \times BW)=\text{Dose}/(\lambda_z \times \text{AUC} \times BW)$.

Analytical method

The serum concentrations of propranolol and atenolol were determined by high-performance liquid chromatography (HPLC) using a Kontron system with a spectrofluorometric detector SFM 25 and pronethalol as an internal standard [15]. Propranolol was extracted from plasma, and samples were injected into a LC-8-DB column (Supelcosil) and then the drug was monitored at an excitation wavelength of 210 nm and emission wavelength of 340 nm. Atenolol was extracted as follows: 125 ng of metoprolol (internal standard) was added to 1 ml of plasma, then the sample was alkalized with 0.5 M sodium hydroxide and precipitated with ethyl acetate for 10 min. Following centrifugation, the organic phase was separated and evaporated at 35°C in nitrogen stream. The residue was dissolved in 200 µl of mobile phase and then 100 µl was added to a column. The column and detector were the same as in the case of propranolol. Atenolol was monitored at an excitation wavelength of 225 nm and emission wavelength of 300 nm. The standard curves were prepared from blank plasma samples from healthy individuals. They were linear over the calibration range of 5–200 (5, 10, 25, 50, 100, 150, 200) ng/ml and 10–1000 (10, 100, 250, 500, 1000) ng/ml for propranolol and atenolol, respectively. At quality control plasma concentrations of 5, 25 and 200 ng/ml for propranolol, and 10, 100, 500, 1000 ng/ml for atenolol, coefficients of variation were less than 10%. The quantification limit was approximately 5 ng/ml and 10 ng/ml for propranolol and atenolol, respectively.

Pharmacodynamic studies

Heart rate and blood pressure were measured over a 24 h period at each time point the concentrations of propranolol and atenolol were estimated. Measurements were always performed prior to the sampling of blood. In each patient three consecutive blood pressure measurements were made after 15 min of supine rest, using a random-zero mercury sphygmomanometer. The disappearance of the fifth phase of Korotkoff sounds was taken as the diastolic pressure. The mean of each set of three measurements was used in the calculations. Throughout the study blood pressure and heart rate were measured in the same arm and by the same observer.

Statistic evaluation

Pharmacokinetic parameters were presented as a mean and standard error (SEM). Statistical comparisons of data with non-normal distribution were performed by the unpaired Wilcoxon's test, whereas analysis of variance ANOVA was applied for data normal distribution. A p value of less than 0.05 was considered significant.

Correlations between systolic and diastolic blood pressure, heart rate and blood serum concentrations of propranolol and atenolol were also determined by calculating the correlation coefficient (r).

Results

Pharmacokinetic studies

There were no statistically significant differences in the mean plasma concentrations of propranolol between three groups of the study. The trend towards elevated plasma concentrations of propranolol was noted in obese patients without hyperlipidaemia (Figure 1). In the case of atenolol, mean plasma concentrations of the drug were lower in obese patients both with and without hyperlipidaemia compared with the lean controls, these differences being statistically significant at 2, 3, 4 and 6 h (Figure 2).

The pharmacokinetic parameters of propranolol are reported in Table 1. A high degree of

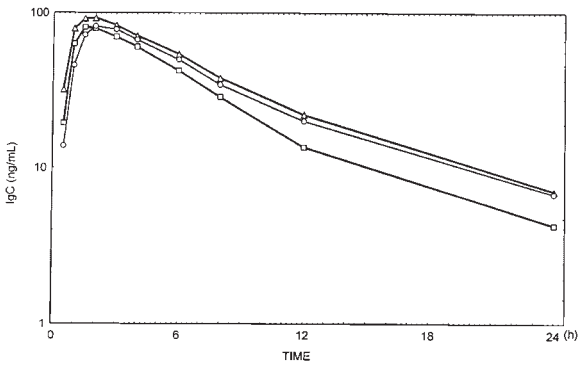

Figure 1. Serum concentrations of propranolol in normolipaemic obese (△), hyperlipidaemic obese patients (○) and in lean controls (□)

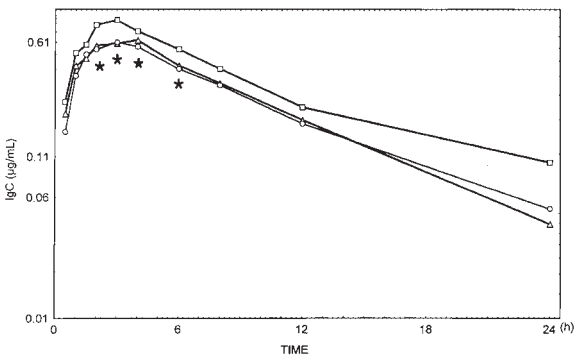

Figure 2. Serum concentrations of atenolol in normolipaemic obese (△), hyperlipidaemic obese patients (○) and in lean controls (□) (*statistical significance: hyperlipidaemic and normolipaemic obese patients vs lean controls)

intersubject variability was observed in the calculated values of pharmacokinetic parameters, with no statistically significant differences between any of the study groups. The largest *AUC* was observed in obese subjects with hyperlipidaemia, and it was increased by 6.5% in comparison with lean controls. C_{max} attained the highest values in obese normolipaemic patients, which were elevated by 19.7% referred to as the controls, whereas t_{max} was the most prolonged in obese hyperlipidaemic patients (by 19.7% in comparison with lean controls). $V_d/(F \times BW)$ of the drug was slightly increased in obese patients with hyperlipidaemia compared with the controls and obese normolipaemic subjects (5.1 ± 1.71/kg for obese with hyperlipidaemia, 4.1 ± 1.91/kg for obese normolipaemic patients, and 5.0 ± 1.21/kg for the controls). $Cl/(F \times BW)$ was reduced in obese normolipaemic subjects as well as in obese with hyperlipidaemia compared with the controls by 30% and 40%, respectively. The $t_{1/2}$ was prolonged in the obese subjects without hyperlipidaemia and the obese with hyperlipidaemia by 21.4% and 47.0%, respectively.

The *AUC* of atenolol was reduced in both groups of obese patients compared with the controls by 48.1% ($p < 0.05$) in patients without hyperlipidaemia and by 50.1% ($p < 0.05$) in hyperlipidaemic ones. C_{max} was the highest in the control group, increased by 21.5% ($p < 0.05$) and 24.1% ($p < 0.05$) compared with obese normolipaemic and hyperlipidaemic patients, respectively. The $V_d/(F \times BW)$ was reduced in obese persons without and with hyperlipidaemia by 36.8% and 36.8%, respectively. The $Cl/(F \times BW)$ of atenolol was decreased in obese nomolipemic by 20.6% ($p < 0.05$) and obese with

Table 1. Mean (± SEM) values of pharmacokinetic parameters of propranolol

Pharmacokinetic parameter (unit)	Group		
	Control	Obese normolipaemic	Obese hyperlipaemic
AUC (ng/ml × h)	1087.7 ± 415.8	498.3 ± 298.8	1158.8 ± 379.1
C_{max} (ng/ml)	79.6 ± 9.2	95.3 ± 15.5	75.9 ± 11.3
t_{max} (h)	2.4 ± 0.2	2.5 ± 0.3	2.9 ± 0.2
k_{el} (h^{-1})	0.32 ± 0.02	0.27 ± 0.04	0.25 ± 0.04
Cl/F (l/h)	73.1 ± 16.4	66.2 ± 22.2	63.4 ± 21.2
V_d/F (l)	356.6 ± 89.5	391.0 ± 165.7	539.5 ± 184.5
$Cl/(F \times BW)$ (l/h/kg)	1.0 ± 0.2	0.7 ± 0.3	0.6 ± 0.2
$V_d/(F \times BW)$ (l/kg)	5.0 ± 1.2	4.1 ± 1.9	5.1 ± 1.7
$t_{1/2}$ (h)	2.4 ± 0.2	2.9 ± 0.3	3.5 ± 0.5

Table 2. Mean (± SEM) values of pharmacokinetic parameters of atenolol

Pharmacokinetic parameter (unit)	Group		
	Control	Obese normolipaemic	Obese hyperlipaemic
AUC (μg/ml × h)	20.0 ± 5.6	10.4 ± 4.1[a]	10.0 ± 3.7[a]
C_{max} (μg/ml)	0.8 ± 0.1	0.6 ± 0.1[a]	0.6 ± 0.1[a]
t_{max} (h)	2.9 ± 0.2	3.1 ± 0.3	3.1 ± 0.3
k_{el} (h^{-1})	0.22 ± 0.02	0.22 ± 0.02	0.23 ± 0.01
Cl/F (l/h)	6.9 ± 1.9	7.8 ± 2.5	6.9 ± 2.0
V_d/F (l)	47.6 ± 12.7	43.6 ± 15.0	43.0 ± 11.1
$Cl/(F \times BW)$ (l/h/kg)	0.10 ± 0.03	0.07 ± 0.01[a]	0.06 ± 0.01[a]
$V_d/(F \times BW)$ (l/kg)	0.7 ± 0.2	0.4 ± 0.1	0.4 ± 0.1
$t_{1/2}$ (h)	4.0 ± 0.6	3.3 ± 0.2	3.5 ± 0.4

[a] Statistical significance ($0 < 0.05$) vs control.

hyperlipidaemia by 28.9% ($p < 0.05$ vs lean controls). The $t_{1/2}$ was shortened in the obese subjects without and with hyperlipidaemia by 17.1% and 12.6%, respectively (Table 2).

Pharmacodynamic studies

Prior to administration of propranolol and atenolol the values of measured cardiovascular parameters were within the normal range. Mean systolic and diastolic arterial blood pressure recorded throughout the 24 h study period are shown in Tables 3 and 4. In all study groups propranolol produced a significant reduction in systolic and diastolic blood pressure compared with the baseline values. The described changes of arterial blood pressure were most prominent in the controls with a maximum between 2 and 4 h. Comparing obese patients with and without hyperlipidaemia it seems that the onset of hypotensive effect occurred earlier in hyperlipidaemic patients. Similar to propranolol, atenolol significantly reduced systolic and diastolic blood pressure, compared with the baseline values taken prior to the drug ingestion, both in the controls and the obese patients. The reduction of the measured blood pressure was best seen between 1 and 3 h after atenolol administration. The reduction of blood pressure was of a similar magnitude in all study groups administered atenolol. Following propranolol administration a significant reduction of heart rate was observed in the controls and obese patients with and without hyperlipidaemia, with the most signifi-

Table 3. The values of pharmacodynamic parameters after propranolol administration

Time (h)	Control			Obese normolipaemic			Obese hyperlipaemic		
	SP	DP	HR	SP	DP	HR	SP	DP	HR
0	125.0 ± 4.2	81.0 ± 2.6	75.6 ± 1.8	132.2 ± 4.7	87.2 ± 2.4	61.4 ± 4.6	130.0 ± 5.6	88.3 ± 2.5	73.7 ± 5.8
0.5	122.2 ± 2.9	81.4 ± 2.5	68.9 ± 1.2[a]	126.7 ± 5.6	84.4 ± 3.2	56.7 ± 3.2[a]	115.8 ± 4.0[a]	88.3 ± 1.0	67.8 ± 4.8
1	116.1 ± 2.2[a]	78.9 ± 2.6	66.3 ± 1.2[a]	122.8 ± 5.9	83.3 ± 3.1	57.1 ± 2.2	113.3 ± 1.7[a]	85.8 ± 1.5	64.5 ± 4.7[a]
1.5	117.5 ± 2.6	78.6 ± 2.8	65.6 ± 1.6[a]	118.9 ± 7.0	83.3 ± 3.7	56.1 ± 2.7	121.7 ± 6.7	90.0 ± 3.4	62.3 ± 5.0[a]
2	112.5 ± 2.7[a]	76.8 ± 2.2[a]	62.7 ± 1.1[a]	117.2 ± 6.7[a]	77.8 ± 4.7[a]	55.2 ± 2.2	115.8 ± 6.0	86.7 ± 1.7	64.0 ± 5.8[a]
3	112.2 ± 2.9[a]	77.5 ± 2.3	61.9 ± 1.4[a]	111.1 ± 4.8[a]	76.7 ± 3.2	51.8 ± 2.4[a]	113.3 ± 5.7	80.8 ± 4.0[a]	63.0 ± 5.2[a]
4	114.2 ± 3.1[a]	74.2 ± 2.3	64.5 ± 1.3[a]	109.4 ± 6.2	70.6 ± 4.3	56.0 ± 3.0	115.0 ± 5.5	79.2 ± 3.7	66.3 ± 6.2
6	113.9 ± 4.2[a]	74.4 ± 2.8[a]	65.8 ± 1.4	122.8 ± 4.7	75.6 ± 3.3	56.0 ± 2.1	120.8 ± 4.4	85.0 ± 3.6[a]	69.3 ± 6.2[a]
8	118.3 ± 3.4	77.8 ± 2.2	65.7 ± 1.1[a]	120.0 ± 5.7	83.3 ± 2.9	56.1 ± 3.2[a]	119.2 ± 4.2	81.7 ± 3.1	65.7 ± 5.1[a]
12	115.6 ± 3.0[a]	72.5 ± 2.7[a]	65.7 ± 2.0[a]	116.1 ± 4.0[a]	71.1 ± 2.5	56.7 ± 3.0	123.3 ± 5.6	83.3 ± 3.1[a]	65.8 ± 5.7[a]
24	119.2 ± 2.7	76.4 ± 2.3	73.3 ± 1.8	120.0 ± 4.5	79.4 ± 3.4	58.6 ± 4.1	120.8 ± 5.2	82.5 ± 1.7	71.0 ± 7.3

SP, systolic blood pressure; DP, diastolic blood pressure; HR, heart rate.
[a] $p < 0.05$ (to the baseline values).

Table 4. The values of pharmacodynamic parameters after atenolol administration

	Control			Obese normolipaemic			Obese hyperlipaemic		
Time (h)	SP	DP	HR	SP	DP	HR	SP	DP	HR
0	125.3 ± 2.8	80.6 ± 2.3	71.4 ± 1.5	129.4 ± 4.3	86.7 ± 2.4	60.8 ± 3.5	129.2 ± 5.7	89.2 ± 4.2	68.5 ± 6.6
0.5	119.7 ± 2.4[a]	78.6 ± 2.1	65.6 ± 1.2[a]	124.4 ± 5.3	85.0 ± 3.5	59.1 ± 2.4	122.5 ± 5.0	85.6 ± 2.0	65.5 ± 4.6
1	115.6 ± 3.7[a]	79.7 ± 3.3	62.7 ± 1.4	116.1 ± 5.6[a]	80.0 ± 3.1[a]	54.2 ± 3.5[a]	114.2 ± 3.5[a]	81.7 ± 1.7	60.5 ± 6.4[a]
1.5	113.3 ± 3.7[a]	76.9 ± 3.0	59.7 ± 0.9[a]	114.4 ± 5.5[a]	78.9 ± 3.0	54.9 ± 3.2[a]	111.7 ± 4.2[a]	78.9 ± 2.7[a]	54.9 ± 3.2[a]
2	106.7 ± 3.0[a]	73.1 ± 2.7[a]	59.5 ± 1.2[a]	116.7 ± 5.4[a]	77.2 ± 3.5	54.7 ± 3.8	110.8 ± 4.4[a]	82.5 ± 3.1	59.3 ± 5.6[a]
3	108.1 ± 3.1[a]	75.8 ± 2.7[a]	59.1 ± 1.4[a]	112.8 ± 5.7[a]	76.1 ± 3.7[a]	52.3 ± 2.6[a]	108.3 ± 1.7[a]	81.7 ± 2.5[a]	59.7 ± 5.5[a]
4	111.7 ± 2.4[a]	74.4 ± 3.0[a]	62.1 ± 1.3[a]	113.3 ± 8.3[a]	78.3 ± 4.6	55.8 ± 3.2	110.8 ± 4.2[a]	84.2 ± 3.0	63.3 ± 5.6
6	111.1 ± 2.4[a]	73.3 ± 2.2[a]	62.6 ± 1.1[a]	112.2 ± 5.8[a]	76.7 ± 3.6[a]	55.2 ± 3.2[a]	115.0 ± 4.3	80.8 ± 1.5	63.8 ± 6.5[a]
8	109.4 ± 2.8[a]	69.4 ± 2.5[a]	60.9 ± 1.2[a]	115.6 ± 4.7[a]	74.4 ± 3.3[a]	52.7 ± 2.9[a]	108.3 ± 3.3[a]	79.2 ± 2.7[a]	65.0 ± 5.0
12	116.1 ± 3.3[a]	72.8 ± 2.5[a]	62.8 ± 1.3[a]	118.9 ± 5.0[a]	79.4 ± 2.9[a]	54.6 ± 3.0[a]	105.0 ± 4.8[a]	71.7 ± 2.4[a]	63.2 ± 6.4
24	1177.5 ± 4.1[a]	78.1 ± 2.6	68.2 ± 1.8	130.0 ± 5.7	83.9 ± 3.3	57.1 ± 3.8	120.8 ± 4.2	83.9 ± 3.3	63.3 ± 4.9

SP, systolic blood pressure; DP, diastolic blood pressure; HR, heart rate.
[a] $p < 0.05$ (to the baseline values).

cant changes seen in the control group. This effect was least prominent in obese patients without hyperlipidaemia, but the initial heart rate value in these patients was the slowest (Table 3). Likewise, atenolol significantly reduced heart rate (Table 4). Most noticeable effects for heart rate were observed from 1.5 to 3 h, and were least marked in obese patients with hyperlipidaemia. However, the baseline heart rate of these patients was the slowest compared with the two study groups.

No significant correlations between the plasma levels of propranolol and atenolol and the measured pharmacodynamic effects was observed.

Discussion

Atenolol and propranolol are extensively used in the therapy of obesity-associated disease states such as arterial hypertension, arrhythmias or coronary heart diseases. Propranolol, a non-selective β-adrenolytic, is a lipophilic drug whereas atenolol, a β1-selective agent, is a hydrophilic drug. Not only do these two agents differ in their lipid solubility but they also differ as regards their renal and hepatic excretion.

The aim of the study was to compare pharmacokinetic parameters and haemodynamic effects of propranolol and atenolol in obese patients with and without lipid disorders. The results of pharmacokinetic studies for the healthy controls were similar to those reported by other investigators [11–13]. In obese subjects both with and without hyperlipidaemia the pharmacokinetics of propranolol and atenolol were altered, most significantly during the elimination phases.

It should be noted that high intersubject variability in pharmacokinetic parameters was observed, and could affect calculations. It was not possible to evaluate total body clearance and volume of distribution since the extent to which the drugs were absorbed was not determined during the study. This means that differences between patient groups might be the result of differences in the extent of absorption of the drugs, which in the case of propranolol is generally accepted to be in the order of 25%–30%, and for atenolol about 40%.

However, assuming that bioavailability does not contribute significantly to differences between patient groups, the more lipophilic drug, propranolol showed a tendency towards a reduced apparent volume of distribution (l/kg) in obese normolipaemic patients when compared with both non-obese controls and obese patients with hyperlipidaemia. With the more water-soluble atenolol there was the tendency towards a reduced apparent volume of distribution (l/kg) in obese patients, irrespectively of concomitant lipid metabolism disturbances, when compared

with the controls. Two of the factors that affect the distribution of drugs are binding to plasma proteins and tissue penetration. Propranolol is 90% bound to α_1-acid glycoprotein, which is present at similar concentration in obese and lean subjects [16]. It is unlikely, therefore, that there are differences between the patient groups with regard to binding of propranolol within the plasma.

The extent to which a drug will distribute into body tissues will depend upon the relative amounts of the different types of tissue. Obese individuals have an increased absolute amount of lean body mass as well as fat tissue in comparison with lean subjects [17]. Forbes *et al*. [18] reported that the lean component of the body in obese patients accounts for 20%–40% of the excess weight. The distribution volume for certain lipophilic drugs such as: benzodiazepines, trazodon and sufentanil are significantly increased in obese subjects. However, other lipophilic drugs such as prednisolone and cyclosporine, have a decreased distribution volume in obese subjects [8]. Their total volume of distribution is increased in obesity, but is lower when calculated relative to body mass. Since an increased body weight in obese subjects involves an increase in lean weight as well as body fat, Cheymol *et al*. [13] suggested that the lipophilic β-adrenoreceptor blockers diffuse less efficiently into adipose tissue than into lean tissue. The excess of lean tissue in obese patients can increase the distribution volume of lipophilic propranolol. Similar conclusions were presented by Bickel [19], who stated that the key factor for storage in adipose tissue is a so-called 'binding competition' between lean and adipose tissue. Hence, storage in adipose tissue is low when binding to lean tissues is high. Distribution of lipophilic β-adrenoreceptor blockers will be dependent on both adipose and lean tissues; their distribution will be restricted and controlled by the sum of the hydrophobic forces and hydrogen bonds they make with lean tissues.

Thus lipophilicity alone cannot account for the pharmacokinetic differences between normal and obese subjects. A combination of biological and physicochemical factors must be involved. However, in the present study the apparent volume of distribution of propranolol was not significantly affected by obesity although there was a trend towards a reduced volume in the normolipaemic obese patients. The relative volume of distribution of lean controls and obese with hyperlipidaemia were comparable.

In the case of atenolol a trend towards some decrease in distribution volume for obese patients with and without lipid disorders was observed. Lipophilicity alone cannot account for all of the differences observed in the distribution volume between obese and lean subjects. Other factors, such as electrical form at physiological pH, haemodynamic effects of drugs and changes of local blood flow may all contribute to altered drug tissue distribution.

The total body clearance determines plasma drug concentration at steady state during drug administration. Hepatic clearance of many drugs may be altered by two major mechanisms: inhibition or induction of the enzymes due to drugs interaction or liver damage, and alteration in hepatic blood flow. In the present study, there was a trend towards a reduced total body clearence of propranolol in obese subjects. In addition, a significant reduction was observed in the total body clearence of atenolol in obese subjects.

The more lipophilic drug propranolol is metabolized in liver. Previous studies have reported that obese persons have impaired liver function due to fatty infiltration [4, 5].

The latter phenomenon could be one of the factors leading to reduced clearance of propranolol in obese subjects. On the contrary, atenolol is mostly excreted via the kidney, and its clearance was also impaired in obese subjects.

Contrary to our observations, Cheymol *et al*. [12] reported an increased clearance of nebivolol in obesity. Nevertheless, the results of Galletti *et al*. [11] suggested that obesity did not influence the pharmacokinetics of water-soluble β-blockers.

The pharmacodynamic effects of propranolol and atenolol observed in obese and lean persons were similar. No significant differences were noted between the pharmacodynamic effect of the two beta-blocking agents in any of the groups; propranolol and atenolol significantly reduced systolic and diastolic blood pressure and a significant reduction in heart rate in each group. The results of the present study suggest

that lipid status does not modify the pharmacodynamic effects of the drugs. However, no significant correlation was observed between plasma levels and the hypotensive effects of propranolol and atenolol.

These findings are consistent with the concept that the plasma concentration of β-blockers is not a reliable predictor of their cardiovascular activity [12, 13].

The results of our study suggest that obesity and concomitant lipid disorders has a minimal effect on the pharmacokinetics of β-blockers. However, the observed differences in the pharmacokinetics did not result in any clinically significant differences in the pharmacodynamics of either drug between obese and non-obese subjects.

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