

## COMPARATIVE PHARMACOKINETICS OF PROPRANOLOL AND ATENOLOL IN PRIMARY HYPERLIPIDEMIA

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The study was aimed to examine the effects of different types of hyperlipidemia on the pharmacokinetics of lipophilic propranolol and hydrophilic atenolol. Thirty subjects were divided into four study groups: normolipemics, hypercholesterolemics, hypertriglyceridemics, and patients with mixed form of hyperlipidemia. The drugs were administered orally at a single dose of 80 mg for propranolol and 100 mg for atenolol, using a cross-over study design. Pharmacokinetic parameters of the drugs were calculated using a noncompartmental open model. The results of the present study demonstrated a possible influence of dyslipidemia on pharmacokinetics of both the lipophilic and hydrophilic drugs. As for the lipophilic drug propranolol, a significant decrease in elimination rate constant was found (from  $0.24 \pm 0.08 \text{ h}^{-1}$  to  $0.16 \pm 0.04 \text{ h}^{-1}$ ,  $p < 0.03$ ) in comparison to normolipemic subjects. In the case of the hydrophilic atenolol, the most marked alterations were also seen in subjects with mixed form of hyperlipidemia, especially significantly lower values of area under the concentration-time curve ( $8950.8 \pm 2060.5 \text{ ng/ml}\cdot\text{h}$  and  $6715.4 \pm 1813.8 \text{ ng/ml}\cdot\text{h}$ ,  $p < 0.05$ ) as well as higher elimination rate constant ( $0.08 \pm 0.03 \text{ h}^{-1}$  and  $0.13 \pm 0.05 \text{ h}^{-1}$ ,  $p < 0.05$ ) in comparison with the controls, respectively. Total body clearance per kg of body weight of propranolol as well as atenolol was not influenced by dyslipidemias. The results of the study indicate that lipid metabolism disturbances might to some extent influence the pharmacokinetics of propranolol and atenolol, with the most significant alterations seen in the patients with mixed form of hyperlipidemia.

**Key words:** *propranolol, atenolol, pharmacokinetics, hyperlipidemia*

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## INTRODUCTION

It was demonstrated that lipid metabolism disorders can affect pharmacokinetic properties of drugs. Previous studies reported the altered kinetics of e.g. doxycycline [13], phenytoin [7], procainamide [16] and lidocaine [26] in experimental, dietary-induced hyperlipidemia and in patients with dyslipidemias.

Propranolol and atenolol are representatives of  $\beta$ -adrenolytic drugs, which are in clinical use in the management of diseases frequently associated with lipid metabolism disorders, i.e. coronary heart disease, cardiac arrhythmias or hypertension. The two drugs selected for the present study exhibit largely different lipid solubility. Out of all known  $\beta$ -adrenolytics, propranolol has the highest lipophilicity (partition coefficient – 20.2), whereas atenolol is a highly hydrophilic drug (partition coefficient of 0.02) [1]. Several authors have reported a dependence of a drug pharmacokinetics on its lipophilicity. Lipophilic drugs such as propranolol are extensively metabolized by the liver while hydrophilic  $\beta$ -blockers, including atenolol, are predominantly excreted by the kidney. Furthermore, propranolol penetrates well into the central nervous system, whereas atenolol does not. The variability in lipophilicity could influence pharmacokinetics of these drugs in dyslipidemic patients [14, 18]. It was also demonstrated that obesity, which is often associated with blood lipid disorders, is one of the conditions modifying the behavior of  $\beta$ -adrenolytics, depending on their lipid solubility [4, 20]. However, studies on the kinetics of  $\beta$ -blockers in dyslipidemic and obese patients did not lead to concluding results. Our previous data suggested that the plasma lipid status could influence both pharmacokinetics and pharmacodynamics of propranolol in hyperlipidemia [28, 29]. To extend the previous studies, we decided to compare pharmacokinetic properties of lipophilic propranolol and hydrophilic atenolol in patients suffering from different forms of primary hyperlipidemia.

## MATERIALS and METHODS

The study was carried out in 30 non-smokers (13 women and 17 men) divided into 4 study groups. The first group consisted of 8 healthy, normolipemic volunteers (total cholesterol  $5.21 \pm 0.44$  mmol/l, triglycerides  $1.23 \pm 0.01$  mmol/l; values considered

as normal: total cholesterol below 5.2 mmol/l, triglycerides below 2.0 mmol/l) aged 24–55 years (mean  $43.2 \pm 10.4$  years). Second group included 6 patients aged  $40.3 \pm 9.2$  years with hypercholesterolemia classified by total cholesterol level of at least 7.76 mmol/l and normal triglycerides level (mean cholesterol  $9.21 \pm 1.13$  mmol/l; triglycerides  $1.41 \pm 0.45$  mmol/l). The group 3 consisted of 8 subjects with hypertriglyceridemia diagnosed by normal cholesterol level and triglycerides exceeding 4.56 mmol/l (mean triglycerides  $12.71 \pm 3.68$  mmol/l; total cholesterol  $6.19 \pm 0.99$  mmol/l), aged  $41.4 \pm 8.8$  years. The fourth study group consisted of 8 subjects with mixed form of hyperlipidemia, with mean total cholesterol level of  $11.26 \pm 2.88$  mmol/l and triglycerides of  $15.28 \pm 11.02$  mmol/l with mean age of  $44.7 \pm 7.4$  years. BMIs (body mass index) in the abovementioned groups were as follow:  $24.0 \pm 2.6$  kg/m<sup>2</sup>,  $26.4 \pm 2.5$  kg/m<sup>2</sup>,  $27.2 \pm 3.8$  kg/m<sup>2</sup>, and  $26.6 \pm 2.7$  kg/m<sup>2</sup>, respectively. The weight of all subjects had been stable for at least 2 months prior to the study period. The diagnosis of lipid metabolism disturbances was established on a basis of thrice measurement of fasting level of blood triglycerides and total cholesterol, with a 7-day interval. During the study period, all subjects remained on a hypolipemic 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 hyperlipidemia were excluded from the study. The study protocol was approved by the Ethics Committee of Pomeranian Academy of Medicine, Szczecin, Poland, and the patients gave written informed consent.

## Sample collection and analytical method

The cross-over design with a 7-day interval was applied to study pharmacokinetics of single doses of propranolol and atenolol. The subjects fasted overnight prior to oral administration of 80 mg of propranolol (Polfa, Poland) or 100 mg of atenolol (Polpharma, Poland). Tablet ingestion was followed by drinking of 200 ml of tap water. A light meal was permitted 3 h after the drug administration, and meals were allowed thereafter with 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 following the morning drug administration. Blood samples were centrifuged and sera were stored fro-

zen at  $-20^{\circ}\text{C}$  until the assays were done. The serum concentrations of propranolol and atenolol were determined by high-performance liquid chromatography (HPLC) using Kontron system with spectrofluorometric detector SFM 25 and pronethalol as an internal standard [15]. The standard curves were prepared from blank serum samples obtained from patients with hypercholesterolemia, hypertriglyceridemia and mixed-form of hyperlipidemia, and were spiked with propranolol and atenolol. The assay was linear over a range of 5–200  $\mu\text{g/l}$  for propranolol and 100–1000  $\mu\text{g/l}$  for atenolol. The detection limit was 5  $\mu\text{g/l}$  and 10  $\mu\text{g/l}$  for propranolol and atenolol, respectively. For quality control, serum drug concentrations of 5, 25, and 200  $\mu\text{g/l}$  were assayed showing coefficients of variation less than 10%. Detailed analytical method for propranolol and atenolol extraction and detection used by our group was published elsewhere [28, 30].

### Pharmacokinetic parameters

Individual concentrations versus time plots for propranolol and atenolol were calculated for each subject using noncompartmental open model, and the following pharmacokinetic parameters were considered. Mean value of maximal serum concentration ( $C_{\text{max}}$ ) and time required to reach  $C_{\text{max}}$  ( $t_{\text{max}}$ ) were calculated from the individual peak blood concentrations of the drugs. The area under the total blood concentration-time curve (AUC) was determined by trapezoidal rule until the last concentration was measured and extrapolated to infinity. The terminal slope ( $\lambda_z$ ) was obtained by non-linear regression of the log blood concentration against time from the last four to six points using quasi-Newton procedure. The elimination half-life ( $t_{1/2}$ ) was calculated using the equation  $t_{1/2} = \ln 2 / \lambda_z$ . The total body clearance per kg of body weight ( $\text{Cl}/\text{BW}/\text{F}$ , where BW – body weight; F – the fraction of the administered dose systematically available) was calculated by equation:  $\text{Cl}/\text{BW}/\text{F} = \text{F} \cdot \text{Dose}/\text{AUC} \cdot \text{BW}$ . The volume of distribution at steady state per kg of body weight ( $V_{\text{dss}}/\text{BW}/\text{F}$ ) was calculated as the volume based on the terminal slope according to the equation:  $V_{\text{dss}}/\text{BW}/\text{F} = \text{F} \cdot \text{Dose} \cdot \text{AUMC}/\text{AUC}^2/\text{BW}$ . Finally mean residence time (MRT) was evaluated from the equation  $\text{MRT} = \text{AUMC}/\text{AUC}$ . The area under the moment curve (AUMC) was calculated from the following equation:

$$\text{AUMC} = \sum_{i=1}^n \frac{Dt(t_{i-1}C_{i-1} - t_iC_i)}{2} + \frac{t_z C_z}{l_z} + \frac{C_z}{l_z^2}$$

### Statistical analysis

Pharmacokinetic parameters were presented as a mean and standard deviation (SD). Statistical comparisons of pharmacokinetic parameters were performed by the unpaired and paired Wilcoxon's test and Student's *t*-test, where appropriate. A *p* value of less than 0.05 was considered significant.

## RESULTS

Body mass index of all studied groups did not differ significantly, and did not reach values characteristic for obesity (i.e.  $> 30 \text{ kg/m}^2$ ). So, in the study non-obese patients were examined, which allowed us to evaluate an influence of lipid metabolism alterations irrespectively of obesity, a state usually associated with hyperlipidemia.

Mean serum concentrations of propranolol during the first 4 h after the administration were decreased in all groups of patients with dyslipidemia as compared with the controls. However, the observed differences did not reach statistical significance (Fig. 1). The most prominent changes were noted in the subjects with mixed form of hyperlipidemia, where propranolol concentrations were the lowest. This trend was observed for up to 8 h of observation. At 12 and 24 h following drug administration, serum concentrations were not significantly elevated in these patients compared to those observed in the normolipemics. In hypercholesterolemic patients, propranolol concentrations were slightly lower during the first 2 h of observation vs. the control group, and afterwards they were elevated. The observed changes were not statistically significant. In the hypertriglyceridemic subjects, serum concentrations of the drug were decreased up to 4th hour, and then they were moderately higher in comparison with normolipemic subjects.

Serum concentrations of atenolol (Fig. 2) were lower during the whole period of observation in the patients with mixed form of hyperlipidemia compared to the healthy controls. At some time points, i.e. at 2, 3, and 24 h following the drug administration, the observed differences reached statistical significance. In hypertriglyceridemic patients, moderately decreased concentrations of atenolol in relation to normolipemic controls were noted, with

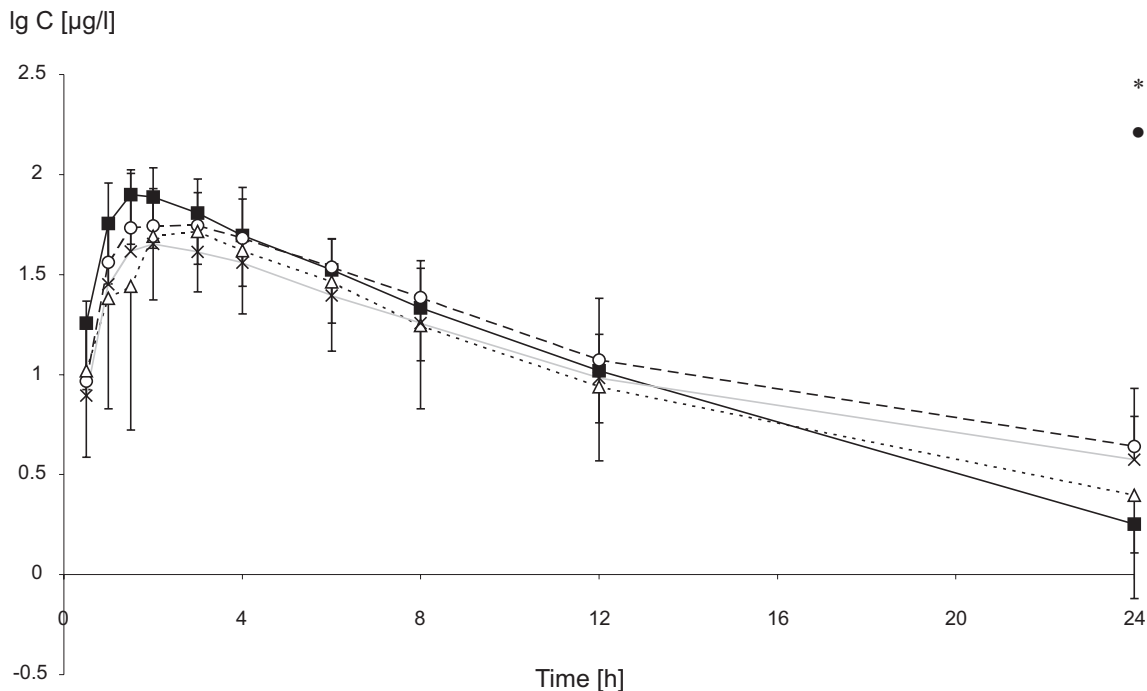


Fig. 1. Median serum concentrations of propranolol in normolipemic controls (■), as well as in patients with hypercholesterolemia (○), hypertriglyceridemia (△) and mixed form of hyperlipidemia (×). (statistical significance: ● hypercholesterolemics vs. controls; \* mixed form of hyperlipidemics vs. controls)

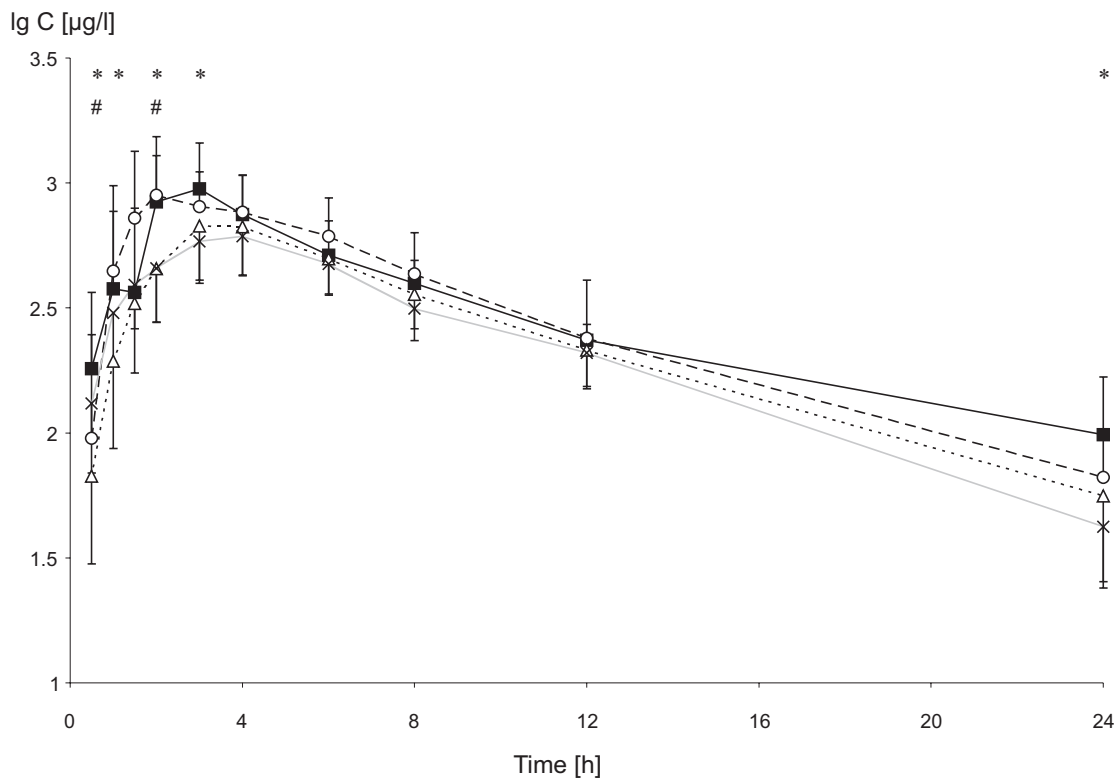


Fig. 2. Median serum concentrations of atenolol in normolipemic controls (■), as well as in patients with hypercholesterolemia (○), hypertriglyceridemia (△) and mixed form of hyperlipidemia (×). (statistical significance: # hyperlipidemics vs. controls; \* mixed form of hyperlipidemics vs. controls)

Table 1. Mean values  $\pm$  SD of pharmacokinetic parameters of propranolol in normolipemic controls (1), as well as in patients with hypercholesterolemia (2), hypertriglyceridemia (3) and mixed form of hyperlipidemia (4)

Parameter (unit)	Group				Statistical significance ( $p < 0.05$ )		
	1	2	3	4	1/2	1/3	1/4
AUC (ng/ml·h)	555.7 $\pm$ 177.6	658.1 $\pm$ 486.4	511.2 $\pm$ 310.0	571.8 $\pm$ 331.4	NS	NS	NS
$\lambda_z$ ( $h^{-1}$ )	0.24 $\pm$ 0.08	0.16 $\pm$ 0.06	0.21 $\pm$ 0.07	0.16 $\pm$ 0.04	NS	NS	< 0.03
$t_{1/2}$ (h)	3.24 $\pm$ 1.25	5.22 $\pm$ 2.80	3.63 $\pm$ 1.01	4.58 $\pm$ 1.44	NS	NS	NS
$C_{max}$ (ng/ml)	102.2 $\pm$ 49.6	78.03 $\pm$ 60.2	73.2 $\pm$ 47.8	56.4 $\pm$ 32.7	NS	NS	< 0.05
$t_{max}$ (h)	1.75 $\pm$ 0.60	2.33 $\pm$ 0.75	2.50 $\pm$ 0.89	2.00 $\pm$ 0.46	NS	NS	< 0.05
MRT (h)	6.23 $\pm$ 1.13	9.29 $\pm$ 3.14	7.59 $\pm$ 1.38	8.07 $\pm$ 3.11	< 0.05	< 0.03	NS
$V_{dss}/BW/F$ (l/kg)	14.6 $\pm$ 8.4	24.5 $\pm$ 19.1	26.2 $\pm$ 22.9	20.4 $\pm$ 13.7	NS	NS	NS
Cl/BW/F (l/h/kg)	2.26 $\pm$ 0.95	2.41 $\pm$ 1.21	3.30 $\pm$ 2.76	2.51 $\pm$ 1.61	NS	NS	NS

NS – statistically not significant

Table 2. Mean values  $\pm$  SD of pharmacokinetic parameters of atenolol in normolipemic controls (1), as well as in patients with hypercholesterolemia (2), hypertriglyceridemia (3) and mixed form of hyperlipidemia (4)

Parameter (unit)	Group				Statistical significance ( $p < 0.05$ )		
	1	2	3	4	1/2	1/3	1/4
AUC (ng/ml·h)	8950.8 $\pm$ 2060.5	9334.7 $\pm$ 3304.3	7579.5 $\pm$ 3304.3	6715.4 $\pm$ 1813.8	NS	NS	< 0.05
$\lambda_z$ ( $h^{-1}$ )	0.08 $\pm$ 0.03	0.11 $\pm$ 0.02	0.11 $\pm$ 0.04	0.13 $\pm$ 0.05	NS	NS	< 0.05
$t_{1/2}$ (h)	9.71 $\pm$ 4.07	6.74 $\pm$ 1.16	7.99 $\pm$ 6.46	5.88 $\pm$ 1.6	NS	NS	< 0.05
$C_{max}$ (ng/ml)	1136.3 $\pm$ 300.2	1117.5 $\pm$ 431.4	803.0 $\pm$ 327.7	684.6 $\pm$ 226.8	NS	NS	< 0.02
$t_{max}$ (h)	2.56 $\pm$ 0.82	1.83 $\pm$ 0.68	2.44 $\pm$ 0.62	2.50 $\pm$ 0.76	NS	NS	NS
MRT (h)	9.31 $\pm$ 1.56	8.53 $\pm$ 1.03	9.34 $\pm$ 1.59	8.77 $\pm$ 1.10	NS	NS	NS
$V_{dss}/BW$ (l/kg)	1.48 $\pm$ 0.33	1.40 $\pm$ 0.43	1.78 $\pm$ 0.71	1.78 $\pm$ 0.57	NS	NS	NS
Cl/BW (l/h/kg)	0.16 $\pm$ 0.03	0.17 $\pm$ 0.06	0.19 $\pm$ 0.07	0.20 $\pm$ 0.06	NS	NS	NS

NS – statistically not significant

statistically significant differences at 0.5 and 2 h following the drug administration. The patients with hypercholesterolemia had comparable levels of atenolol as the controls.

The calculated pharmacokinetic parameters of propranolol are presented in Table 1. As compared to the normolipemic controls, AUC in all study groups did not differ statistically significantly. The smallest  $V_{dss}/BW$  was noted in the controls but the difference was not significant compared to the patients with dyslipidemias. In hypertriglyceridemic group,  $t_{max}$  was insignificantly prolonged by 43% and  $C_{max}$  was moderately lower by 28% in comparison with the normolipemic subjects. MRT in the patients with hypercholesterolemia and hyper-

triglyceridemia were significantly prolonged by 49% ( $p < 0.05$ ) and 22% ( $p < 0.03$ ), respectively, as compared to the controls. In patients with mixed form of hyperlipidemia,  $V_{dss}/BW$  was increased, although no statistical difference was noted. In this group,  $C_{max}$  and  $\lambda_z$  were the lowest of all study groups and  $t_{max}$  was prolonged by 14% ( $p < 0.05$ ) as compared to control volunteers. The last three results differed significantly from those in group 1. The  $t_{1/2}$  and MRT of propranolol were prolonged in comparison with the normolipemics, but the differences were not statistically significant. Hypercholesterolemic patients were characterized by an increase in propranolol  $V_{dss}/BW$  by 90% in comparison to group 1. The  $t_{1/2}$  was prolonged by 61% as

well as the MRT by 49% ( $p < 0.05$ ) in hypercholesterolemic patients as compared to the controls. The observed  $C_{\max}$  was reduced by 27% as compared to normolipemics. However, the differences in the evaluated pharmacokinetic parameters did not reach statistical significance except for MRT. The marked intersubject differences in serum concentrations of propranolol could contribute to difficulties in demonstrating statistical significance of the results.

Table 2 shows the pharmacokinetic parameters of atenolol in all study groups. The main trend of the changes in atenolol pharmacokinetic parameter was similar in all the dyslipidemic groups as compared to normolipemic controls. Statistically significant differences were observed only in the patients with mixed form of hyperlipidemia. In this group, AUC and  $C_{\max}$  decreased by 25% ( $p < 0.05$ ) and 40% ( $p < 0.02$ ), respectively. A significant increase in  $\lambda_z$  by 62% ( $p < 0.05$ ) was found as well as a shortening of  $t_{1/2}$  by 40% ( $p < 0.05$ ) in the patients with mixed form of hyperlipidemia as compared to normolipemic controls.  $V_{\text{dss}}/\text{BW}$  was insignificantly increased by 29% in subjects with mixed form of hyperlipidemia and in patients with hypertriglyceridemia, while it was slightly decreased (by 9%) in hypercholesterolemics as compared to the controls. Likewise, MRT of atenolol in all groups of dyslipidemic patients and controls did not differ significantly.

## DISCUSSION

Atenolol and propranolol are extensively used in the therapy of lipid metabolism associated disease states such as arterial hypertension, arrhythmias or coronary heart disease. Propranolol, a non-selective  $\beta$ -adrenolytic, is a lipophilic drug, whereas atenolol, a  $\beta_1$ -selective agent, is a hydrophilic drug. These two agents differ in lipid solubility and elimination route, i.e. renal and hepatic for atenolol and propranolol, respectively.

The results of present pharmacokinetic studies for the healthy controls were similar to those reported by other investigators, except for higher values of total body clearance of propranolol [6, 8, 22]. The obtained data may be influenced by the age limit of up to 55 years, which was established prior to the study. In all forms of hyperlipidemia, the pharmacokinetics of propranolol and atenolol were altered, most significantly in the patients with mixed form of hyperlipidemia. It should be noted

that a high intersubject variability in pharmacokinetic parameters was observed, and this could affect calculations. So, potential differences could be classified as trends only in some aspects. The foregoing observations are consistent with the data reported by Cheymol et al. [4], Duchateau et al. [6], Sirtori et al. [22] and Galletti et al. [10]. Some of the observed differences could be ascribed to genetic variations of propranolol metabolizing enzymes [23].

The lipophilic drug propranolol tended to have increased volume of distribution at steady state and prolonged mean residence time in the subjects with hypercholesterolemia, as compared with normolipemic controls. In patients with mixed form of hyperlipidemia, a decrease in maximal concentration as well as elimination rate constant were noted. In subjects with hypercholesterolemia, only mean residence time was prolonged significantly.

As for the hydrophilic drug atenolol, significant changes of pharmacokinetic parameters were observed solely in the patients with mixed form of hyperlipidemia. These patients were characterized by a markedly reduced area under the time-concentration curve, lower maximal drug serum concentrations and elimination half-lives, whereas elimination rate constant and total body clearance were higher in comparison to the controls. Comparison of pharmacokinetics of propranolol and atenolol revealed differences in the pattern of changes in some pharmacokinetic parameters. Elimination rate constant for atenolol tended to be higher in all dyslipidemic groups as compared to normolipemic controls, whereas the elimination rate constant values of propranolol were lower. In patients with mixed form of hyperlipidemia, the differences in elimination rate constant for both propranolol and atenolol reached statistical significance compared to normolipemic controls. Elimination half-life was prolonged for propranolol and shortened for atenolol in all dyslipidemic groups in comparison with normolipemics. The above changes were most pronounced in patients suffering from hypercholesterolemia and mixed form of hyperlipidemia, but in the case of atenolol only in patients with mixed form of hyperlipidemia the changes were significant. Nevertheless, some alterations in the pharmacokinetic parameters of propranolol paralleled those of atenolol. Total body clearance per kg of body weight tended to be increased in all studied groups, with most prominent changes in the sub-

jects with mixed form of hyperlipidemia for atenolol and in hypertriglyceridemics for propranolol. Likewise, mean volume of distribution at steady state for atenolol and propranolol were insignificantly increased in patients with mixed form of hyperlipidemia and hypertriglyceridemia. Similarly, maximal drug concentrations were highest in normolipemic controls and significantly decreased in patients with mixed form of hyperlipidemia.

Kinetic studies of drugs in patients with dyslipidemia suggest that lipophilic drugs are bound to serum lipids, that may act as an additional depot. This has been proven for phenytoin [5], chlorpromazine and sulphamerazine [3] as well as doxycycline [27]. Hydrophilic drugs, e.g. oxytetracycline [27] and procainamide [11] behave in opposite way, most probably due to displacement of the drug from albumin binding sites by free fatty acids. Some drugs, e.g. digoxin, despite their hydrophilic nature, behave like a lipophilic substance in a hyperlipidemic state, which is probably due to their overall physicochemical properties. Similar pharmacokinetic results obtained after oral and intravenous administration of digoxin in hyperlipidemia [12, 17] indicate that the observed changes are not caused by differences in absorption but may be related to alterations in lipid fraction concentrations in serum. Our previous studies have shown that hypolipemic therapy can induce changes in the pharmacokinetics of propranolol, depending on the type of lipid metabolic disorders. The most pronounced alterations, such as an increase in the volume of distribution, were observed in patients with hypertriglyceridemia, whereas hypocholesterolemic therapy did not significantly affect the pharmacokinetics of the drug [28].

The results of the present study confirmed the general trend observed in subjects with different forms of dyslipidemia treated with lipophilic and hydrophilic drugs. As for lipophilic propranolol, the most pronounced changes were observed in patients with mixed form of hyperlipidemia with a trend towards an increase in volume of distribution at steady state and mean residence time. Also a decrease in elimination rate constant was noted in comparison to the normolipemic controls. These data may indicate that lipids circulating in plasma may act as an additional depot. These observations are in keeping with the previously published reports [3, 5, 27]. Approximately 91% to 96% of propranolol can be bound to serum albumin or other

proteins, mainly to  $\alpha_1$ -acid glycoprotein and lipoproteins [19, 21]. Variations in serum binding are correlated to serum concentrations of  $\alpha_1$ -acid glycoprotein, whose level can be modified in various disease states. The effects of hyperlipidemia on the concentration of  $\alpha_1$ -acid glycoprotein in plasma are not known. So, the altered distribution of propranolol in the present study may not only depend on circulating lipids but also on  $\alpha_1$ -acid glycoprotein. It is apparent that the elimination of certain drugs is not limited to the free drug delivered to the liver because their extraction ratio is greater than their free fraction. In fact, there are examples such as the elimination of propranolol in humans, in which clearance is essentially independent of binding in blood. Hepatic clearance of many drugs may be altered by two major mechanisms: inhibition and induction of the enzymes due to drug interactions or liver damage or alteration in hepatic blood flow. Lipophilic propranolol is metabolized in the liver. Previous studies indicated an impaired liver function in persons with fatty infiltration [2, 24]. The latter phenomenon could be one of factors leading to propranolol clearance reduction in obese subjects. Metabolism of propranolol, which is a high-clearance drug, depends on liver blood flow. The extraction ratio, which is 0.7, is influenced by many factors, such as age, diet, physical exercise, smoking habits and liver diseases [9]. However, there is no data whether hyperlipidemia affects liver blood flow. Recent reports suggest that dyslipidemias *per se*, especially those related to LDL cholesterol, might reduce cardiac output independently of the atherogenic properties [25]. Reduced cardiac output, and, thus, liver blood flow in patients with hypercholesterolemia could contribute to slower elimination of propranolol in those patients during the study.

In the case of hydrophilic atenolol, most marked alterations were also seen in subjects with mixed form of hyperlipidemia, especially as lower values of area under the concentration-time curve and increase in elimination rate constant in comparison with the controls. Our data are confirmed by observations of other authors with hydrophilic drugs, i.e. doxycycline [27] and procainamide [11], suggesting that circulating free fatty acids could displace drugs from binding sites on albumin. Contrary to propranolol, atenolol is mostly excreted through kidneys, and its elimination could not only be influenced by displacement of the drug from albumin,

but also by alterations in renal blood flow in patients with hyperlipidemia.

In conclusion, the results of the study suggest that lipid metabolism changes might influence the pharmacokinetics of lipophilic propranolol and hydrophilic atenolol. However, the observed differences in the case of hypercholesterolemic and in hypertriglyceridemic patients mostly lacked statistical significance. The most significant alterations were seen in patients with mixed form of hyperlipidemia administered atenolol, in which an enhanced elimination of the drug was observed. Since  $\beta$ -adrenolytic drugs are administered to patients with coronary artery disease, cardiac arrhythmias and hypertension, i.e. disease states which are frequently associated with changes in plasma lipids, the latter, especially mixed form of hyperlipidemia, may affect pharmacokinetics of  $\beta$ -adrenolytics, and, thus, also their clinical effects.

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