J. Pharm. Pharmacol. 1990, 42: 344–348
Received September 4, 1989



# Comparison of Propranolol and Sotalol Pharmacokinetics in Obese Subjects

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**Abstract**—Six obese subjects (mean ± s.d.: 145·1 ± 16·7% of ideal body weight) were randomly assigned to a single i.v. dose either of (±)-propranolol base (0·108 mg $kg^{-1}$ of ideal body weight) or of (±)-sotalol base (1·06 mg $kg^{-1}$ of ideal body weight). Each subject received the other drug 7 days later. Pharmacokinetic parameters were compared with those obtained previously in non-obese control subjects. In obese subjects, the pharmacokinetic data calculated for sotalol were comparable with those measured in controls (total body clearance = 9·4 ± 2·9 L $h^{-1}$; volume of distribution during the terminal phase = 79·8 ± 19·8 L or 0·9 ± 0·2 L $kg^{-1}$; terminal half-life = 6·2 ± 1·6 h). For propranolol, total clearance (44·3 ± 15·9 L $h^{-1}$) and volume of distribution (230·5 ± 48·2 L or 2·7 ± 0·7 L $kg^{-1}$) were significantly less than control values. The terminal half-life (3·9 ± 1·1 h), was not significantly increased. These results could be explained by altered tissue blood flow and a decreased metabolic capacity of the liver in obese subjects.

The pathophysiological changes accompanying obesity can modify drug pharmacokinetics both in drug distribution and in drug elimination (Cheymol 1988). Recent research has shown that for highly lipophilic substances, e.g. certain benzodiazepines (Abernethy et al 1984) and lignocaine (Abernethy & Greenblatt 1984), the total volume of distribution (in L) was increased in obese subjects and that the half-life of elimination was prolonged. Conversely, the pharmacokinetics of molecules which were not very lipid soluble such as antipyrine (Abernethy et al 1981a) and digoxin (Abernethy et al 1981b) were not significantly modified by obesity. β-Adrenoceptor blocking drugs are used in the treatment of systemic hypertension and coronary heart disease, both disease states in which obesity is a risk factor. Until now, few pharmacokinetic studies have been devoted to these substances in obese subjects. For propranolol, Bowman et al (1986) reported an increase in the total volume of distribution and half-life of elimination in the obese subject, as might be expected with such a highly lipophilic molecule.

However, when we compared 12 obese subjects with healthy controls, we found a significant decrease in the volume of distribution (both in L and in L $kg^{-1}$) and in total plasma clearance for propranolol (Cheymol et al 1987). It therefore appears that factors other than lipid solubility may be involved in the pharmacokinetics of β-blocking drugs in obese individuals.

In this investigation we compared the pharmacokinetics of two drugs of opposite solubility in the same obese patients, in order to determine the importance of lipophilicity relative to other factors. We chose propranolol which is the most lipophilic of the group and sotalol which is markedly hydrophilic (Woods & Robinson 1981). The results of our study were then compared with those previously obtained in healthy non-obese volunteers, under the same experimental conditions (Poirier et al 1981; Cheymol et al 1987)

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## Materials and Methods

*Subjects*

The present study included six obese subjects (5 women and 1 man, aged 28 to 46 years, weighing 73 to 102 kg). Ideal body weight (IBW) was defined (from life insurance tables, Anonymous 1959) as: IBW = "X" kg + 2·3 kg/2·5 cm over 152 cm in height, where "X" = 45·5 (female) or 50·0 (male). Per cent IBW was defined as the ratio of actual body weight to IBW, multiplied by 100. Body mass index (BMI), defined as weight in kg/height$^2$ in metres, was also calculated (Table 1).

A pre-study medical history, physical examination and laboratory tests were performed for each subject, and all had normal hepatic and renal functions. No ECG abnormalities and no contraindications to β-blocking drugs were noted. All the subjects had a stable weight for at least 2 months before the trial and they had not taken any medication 14 days before entering the study. All subjects gave their informed consent. The design of the trial had been accepted by the Saint-Antoine Hospital ethics committee.

*Study design*

After an overnight fast the subjects remained supine and received a single i.v. administration of either propranolol or sotalol in random order with an interval of 7 days between the two administrations. The i.v. doses of (±)-propranolol base (0·108 mg $kg^{-1}$) and (±)-sotalol base (1·064 mg $kg^{-1}$) were calculated for each subject as a function of IBW.

The same dilutions of commercially available injectable solutions of propranolol (Avlocardyl 5 mg) and sotalol (Sotalex 20 mg) in saline were used for all subjects. The drugs were infused with an electric syringe at a flow rate of 1·878 mL $min^{-1}$ over 8 to 13 min. The propranolol and sotalol doses ranged from 5·1 to 8·7 mg and from 50·9 and 85·4 mg, respectively, expressed as the base.

Table 1. Physical and Biochemical characteristics of obese subjects. C = creatinine ($\mu$mol $L^{-1}$)

| Subj. | Sex | Age (y) | Weight (kg) | % IBW | BMI | ALP (IU) | $\gamma$ GT (IU) | C | AAG (mg $L^{-1}$) | HSA (g $L^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 29 | 73 | 131·2 | 27·5 | 28 | 8 | 76 | 631 | 40·5 |
| 2 | F | 35 | 102 | 164·3 | 35·3 | 46 | 25 | 98 | 570 | 36·1 |
| 3 | F | 44 | 74 | 156·4 | 31·2 | 38 | 28 | 68 | 585 | 36·5 |
| 4 | M | 28 | 96 | 119·3 | 28·0 | 46 | 18 | 88 | 480 | 39·9 |
| 5 | F | 35 | 96 | 154·6 | 33·2 | 66 | 8 | 81 | 640 | 38·4 |
| 6 | F | 46 | 87 | 146·7 | 31·2 | 77 | 19 | 50 | 447 | 32·7 |
| Mean ± s.d. | | 36 ± 7 | 88 ± 12 | 145 ± 17 | 31 ± 3 | 50 ± 18 | 18 ± 8 | 77 ± 17 | 559 ± 79 | 37 ± 3 |

Heart rate and blood pressure were monitored (Dinamap TM 1846) every 30 min over 8 h, and cardiac output was measured at rest by a non-invasive method (echocardiography, Diasonics Vingmed CV 700) before administration of the drug, and also 2 and 6 h after the end of the infusion (Hinderliter et al 1987).

Venous blood was collected from the opposite arm before infusion, and at 0, 5, 10, 15, 30 and 45 min, and 1, 1·5, 2, 4, 6, 8, 10, 24 h post infusion. Samples were centrifuged and plasma was stored at −20°C until assayed. All the plasma concentrations were expressed in terms of propranolol or sotalol-base.

*Assays*

Plasma propranolol and sotalol concentrations were determined by specific high-performance liquid chromatographic (HPLC) methods (Lo et al 1982; Poirier et al 1986). The limits of accurate determination were 1 and 10 ng $mL^{-1}$, respectively. Serum concentrations of $\alpha_1$-acid glycoprotein (AAG) and protein binding of propranolol were also measured.

The analytical method used to measure sotalol concentrations was simpler and faster than that used in the previous study on healthy volunteers (Poirier et al 1981), but the resolution was the same and therefore this modification of the HPLC method should not change the results. The two methods were twice tested in the same plasma samples and the estimates of plasma sotalol were not significantly different.

Protein binding was determined by equilibrium dialysis using Teflon microcells (200 $\mu$L Dianorm), and a semipermeable membrane (mol. wt cutoff 12000, Union Carbide). Serum samples collected just before infusion were supplemented with tracer amounts of [$^3$H](±)-propranolol (Amersham; specific gravity 16·4 Ci $mmol^{-1}$; purity 98%). After completion of dialysis over 3 h at 33°C, per cent bound drug was calculated as follows: [(d $min^{-1}$ B − d $min^{-1}$A)/d $min^{-1}$B] × 100, where d $min^{-1}$ B is, for total drug, the number of disintegrations per minute in the protein compartment and d $min^{-1}$ A, the number of disintegrations per minute in the buffer compartment.

AAG concentrations were measured with a Beckman Immunochemistry System ICCTM II Nephelometer based on nephelometric measurements using the AAG reagent test kit (Ref. 449490). In addition, standard clinical laboratory tests were done on serum to determine alkaline phosphatase (ALP), gamma glutamine transferase ($\gamma$-GT), creatinine and albumin (HSA) (Table 1).

*Pharmacokinetic and statistical analysis*

The plasma propranolol and sotalol concentrations measured during the 24 h following i.v. administration were analysed according to an open two-compartment model. Calculations were performed using an iterative non-linear least-squares fitting program with equal weighting factor (Gomeni 1984). The following pharmacokinetic parameters were determined: elimination half-life ($t_{\frac{1}{2}}$), area under the concentration-time curve (AUC) by the trapezoid method and extrapolated to infinity ($AUC_o^\infty$) by adding the value of the last measured concentration divided by the slope of the terminal phase $\beta$, total body clearance ($CL = dose/AUC_o^\infty$), and apparent volume of distribution ($V\beta = CL/\beta$, where $\beta = 0{\cdot}693/t_{\frac{1}{2}}\beta$). Student's $t$-test was used to assess significance at a level of $P < 0{\cdot}05$

## Results

*Effects on cardiovascular parameters*

Comparison of the mean values of heart rate (HR), systolic (SBP) and diastolic (DBP) pressures and cardiac index (CI) before and after intravenous administration of propranolol or sotalol did not show any significant variation (Table 2).

*Biochemical data*

In obese subjects, in comparison with previous data in healthy volunteers (Cheymol et al 1987), serum AAG

Table 2. Mean ± s.d values of cardiac index (CI, L $min^{-1}m^2$), heart rate (HR, beats $min^{-1}$), systolic blood pressure (SBP) and diastolic blood pressure (DBP (mmHg)) at t = 0, at 2 h and 6 h after infusion of drug.

| | T = 0 h | | T = 2 h | | | T = 6 h | | |
|---|---|---|---|---|---|---|---|---|
| | CI | HR | SBP/DBP | CI | HR | SBP/DBP | CI | HR | SBP/DBP |
| Propranolol | 2·78 ± 0·75 | 64 ± 7 | 144 ± 26/82 ± 20 | 2·73 ± 0·83 | 60 ± 10 | 139 ± 27/71 ± 26 | 2·92 ± 0·83 | 68 ± 11 | 141 ± 26/71 ± 16 |
| Sotalol | 2·73 ± 0·63 | 63 ± 6 | 149 ± 20/87 ± 16 | 2·60 ± 0·66 | 59 ± 8 | 135 ± 32/71 ± 18 | 2·81 ± 0·83 | 66 ± 9 | 137 ± 35/75 ± 24 |

Table 3. Pharmacokinetic parameters after i.v. propranolol administration.

| Subject No | Dose (mg) | $AUC_0^\infty$ ($\mu g\ L^{-1}h$) | $t_{\frac{1}{2}}\beta$ (h) | Vβ (L) | Vβ ($L\ kg^{-1}$) | CL ($L\ h^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | 6·0 | 83·4 | 2·7 | 280·1 | 3·8 | 71·9 |
| 2 | 6·6 | 243·6 | 5·4 | 211·2 | 2·1 | 27·1 |
| 3 | 5·1 | 147·9 | 3·4 | 169·3 | 2·3 | 34·5 |
| 4 | 8·7 | 224·0 | 3·7 | 207·2 | 2·2 | 38·8 |
| 5 | 6·7 | 163·1 | 5·0 | 296·5 | 3·1 | 41·1 |
| 6 | 6·4 | 122·7 | 2·9 | 218·4 | 2·5 | 52·2 |
| mean (±) s.d. | 6·6 ±1·2 | 164·1 ±60·7 | 3·9 ±1·1 | 230·5 ±48·2 | 2·7 ±0·7 | 44·3 ±15·9 |

Table 4. Pharmacokinetic parameters after i.v. sotalol administration

| Subject No. | Dose (mg) | $AUC_0^\infty$ ($mg\ L^{-1}h$) | $t_{\frac{1}{2}}\beta$ (h) | Vβ (L) | Vβ ($L\ kg^{-1}$) | CL ($L\ h^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | 59·2 | 7·5 | 6·1 | 69·5 | 1·0 | 7·9 |
| 2 | 66·0 | 12·4 | 8·4 | 64·2 | 0·6 | 5·3 |
| 3 | 50·9 | 5·3 | 5·0 | 69·3 | 0·9 | 9·6 |
| 4 | 85·4 | 8·2 | 7·8 | 117·1 | 1·2 | 10·4 |
| 5 | 66·0 | 7·2 | 5·4 | 71·7 | 0·7 | 9·2 |
| 6 | 63·2 | 4·5 | 4·3 | 86·9 | 1·0 | 14·0 |
| mean (±) s.d. | 65·1 ±11·4 | 7·5 ±2·8 | 6·2 ±1·6 | 79·8 ±19·8 | 0·9 ±0·2 | 9·4 ±2·9 |

concentrations were not significantly different (559±79 mg $L^{-1}$ in obese vs 520±87 mg $L^{-1}$), but serum HSA decreased significantly (37·4±2·9 g $L^{-1}$ in obese vs 42·5±3·1 g $L^{-1}$; $P<0·02$). Percentage of bound propranolol did not differ between the obese and control groups (89·6±1·8% in obese vs 88·3±1·6%). The values of serum ALP, γ-GT and creatinine were in the normal range (Table 1).

*Pharmacokinetic parameters*

Individual results of pharmacokinetic calculations are listed in Tables 3 and 4, for propranolol and sotalol, respectively.

Concerning propranolol, mean values (±s.d.) were $t_{\frac{1}{2}}\beta = 3·9 \pm 1·1$ h, CL = 44·3±15·9 L $h^{-1}$, and Vβ = 230·5±48·2 L and corrected for total body weight (Vβ $kg^{-1}$): 2·7±0·7 L $kg^{-1}$.

The pharmacokinetic parameters for sotalol were: $t_{\frac{1}{2}}\beta = 6·2 \pm 1·6$ h, CL = 9·4±2·9 L $h^{-1}$, and Vβ = 79·8±19·8 L or 0·9±0·2 L $kg^{-1}$.

## Discussion

This study concerns the pharmacokinetics of two β-adrenoceptor blocking drugs of opposite solubility. It was conducted according to a cross over design in young obese subjects (28 to 46 years) presenting moderate overweight (119 to 164% of ideal weight).

For sotalol, the results observed in the obese subjects did not significantly differ from those which we previously found in healthy volunteers (Poirier et al 1981), i.e.: $t_{\frac{1}{2}}\beta = 7·3 \pm 1·1$ h, CL = 7·0±2·2 L $h^{-1}$ and Vβ = 67·0±7·8 L or 1·1±0·1 L $kg^{-1}$. These facts are readily explained for a β-blocking drug which is not very lipophilic (Woods & Robinson 1981), not bound to plasma protein and primarily excreted in the kidney as the unchanged drug (Schnelle et al 1979). A review of the literature shows that for hydrophilic drugs, the total volume of distribution (in L) is not significantly increased in obese individuals (Abernethy et al 1981a, b). For drugs primarily cleared through the kidney, total plasma clearance as well as renal clearance are not decreased in obese individuals, they may even be increased (Bauer et al 1985; Yost & Derendorf 1986). Furthermore Messerli et al (1983) did not observe any modification in renal blood flow in obese subjects.

In the same subjects, we also studied the pharmacokinetic properties of propranolol which, in contrast to sotalol, is highly lipophilic (Woods & Robinson 1981), highly bound to plasma protein and with a high hepatic clearance (Kornhauser et al 1978). The results observed in the obese subjects of this study did not significantly differ from the results obtained in a previous study (Cheymol et al 1987), in which the pharmacokinetic parameters of i.v. propranolol and the percentage of bound drug were determined in 12 obese subjects and 12 normal volunteers. In this former comparative study we had found the following values in obese subjects: Vβ = 234·3±70·4 L or 2·1±0·5 L $kg^{-1}$; CL = 57·5±18·3 L $h^{-1}$; $t_{\frac{1}{2}}\beta = 3·5 \pm 0·9$ h, and a percentage of bound propranolol equal to 90·1±3·1%. The parameters calculated in normal volunteers were: Vβ = 340·7±89·1 L or 5·1±1·3 L $kg^{-1}$; CL = 75·9±15·4 L $h^{-1}$; $t_{\frac{1}{2}}\beta = 3·1 \pm 0·9$ h, and 88·3±1·6% of bound propranolol.

This showed that the values of the volume of distribution (in L and L $kg^{-1}$) and total plasma clearance observed in obese subjects in both of these studies were significantly lower than those in the control subjects; the half-life of elimination and the percentage of bound propranolol did not differ between obese and healthy subjects.

The group of obese subjects of this study (28–46 years; 1M/5F) was not matched in terms of age range and sex ratio to the control group in our previous study on propranolol pharmacokinetics (20–25 years; 9M/3F). Age and sex do not

appear to influence the pharmacokinetics of propranolol in non-obese subjects. Schneider et al (1980) did not find differences in plasma propranolol concentrations when they compared healthy subjects of 63–81 years to those aged 19–25 years. In studies by Vestal et al (1979) and Kornhauser et al (1978) the volume of distribution and the systemic clearance of propranolol did not appear to be related to age in the 21 to 55 years range. Finally Walle et al (1989), after i.v. dosing of propranolol, reported no significant difference between men and women in the volume of distribution, half-life, systemic clearance and protein binding. There are fewer data available on the effects of age and sex on the pharmacokinetics of propranolol in the obese. In our previous study (Table II, Cheymol et al 1987) the reductions in distribution volumes in the obese subgroups appeared to increase with the female/male ratio, however these differences did not reach significance. Additional obese male subjects would be needed to clarify this point.

Our results appear to differ from several publications on the pharmacokinetics of lipophilic substances in obese individuals. Abernethy & Greenblatt (1984) and Abernethy et al (1984), showed an increase in the total volume of distribution (as L) in obese individuals for certain benzodiazepines and lignocaine. The total volume of distribution of $\beta$-blocking drugs increases with the water : octanol partition coefficient (Guidicelli & Witchitz 1983). However, Bickel (1984) demonstrated the absence of correlation between the lipophilic nature of a drug and its storage in adipose tissue. Consequently, factors other than lipophilicity must be taken into account to explain the tissue distribution of these drugs, for example binding to protein and regional blood flow.

Propranolol is essentially bound to $\alpha_1$-acid glycoprotein (Glasson et al 1980). We did not observe a significant difference in either of our studies between the percentage of the binding of propranolol between obese ($89{\cdot}6 \pm 1{\cdot}8\%$) and healthy volunteers ($88{\cdot}3 \pm 1{\cdot}6\%$). The same result has been found by Bowman et al (1986). Benedek et al (1983, 1984) observed a decrease in the free propranolol fraction only in excessively overweight subjects. The significant decrease in apparent absolute volume of distribution of propranolol in obese subjects in our studies therefore can not be explained by a decrease in its free fraction.

A modification in regional blood flow could be proposed to explain the altered tissue distribution of propranolol in the obese. According to studies in dogs, activation of the sympathetic nerves and noradrenaline administration induce changes in the vascular resistance of adipose tissues. These effects are the combined results of $\alpha$-adrenergic vasoconstriction and $\beta$-adrenergic vasodilation. Propranolol and practolol potentiate vasoconstriction induced by noradrenaline administration or sympathetic nerve stimulation (Belfrage 1978). Therefore it is possible that a vasoconstrictive effect induced by $\beta$-blocking drugs in adipose tissue could restrict the tissue distribution of a highly lipid soluble substance such as propranolol, without modifying the distribution of sotalol which already has a restricted tissue diffusion because of its weak lipid solubility.

The plasma clearance of a substance with a high hepatic extraction coefficient, such as propranolol, depends on hepatic blood flow rather than on the metabolic activity of the liver in subjects with an intact liver function (Weiss et al 1978). Messerli et al (1983) in haemodynamic studies conducted in obese individuals, did not observe any alteration in hepatic blood flow. Furthermore, with propranolol and subjects at rest, we did not observe any significant variation in cardiac output with respect to base line values.

The decrease in total plasma clearance of propranolol could therefore be the consequence of altered metabolic capacity in obese subjects. Indeed, Braillon & Capron (1983) observed that 90% of the obese subjects in their study presented histological hepatic alterations which had not been indicated by routine liver function tests (Braillon et al 1985). Pirttiaho et al (1988) demonstrated that in subjects with fatty infiltration of the liver, the rate of elimination of propranolol was decreased due to altered enzymatic function rather than to a decrease in hepatic blood flow.

The simultaneous decrease in volume of distribution and total plasma clearance of propranolol (in obese subjects compared with healthy controls) explains why we did not observe any modification in its elimination half-life.

In conclusion, we did not observe any modification, in obese subjects, in the pharmacokinetic parameters of sotalol, which is not very lipid soluble and which is essentially cleared by the kidney. In contrast, in these same subjects, the pharmacokinetics of propranolol, which is highly lipid soluble and has a high metabolic clearance, were different from those in healthy volunteers. We propose that these modifications could be due to changes in tissue perfusion and metabolic capacity of the liver in obese individuals.

*Acknowledgements*

The authors would like to thank Mrs M. Lebot for her excellent technical assistance.

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