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Obesity influences propranolol pharmacokinetics in patients undergoing coronary artery bypass grafting employing cardiopulmonary bypass

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Propranolol plasma levels and kinetic disposition may be altered by hypothermic cardiopulmonary bypass (CPB-H). We investigated the potential influence of obesity on propranolol pharmacokinetics in patients undergoing coronary artery bypass grafting employing CPB-H. Fifteen patients, receiving propranolol perorally pre- (10-40 mg, 2-3 times a day) and post-operatively (10 mg, once a day) were distributed in two groups, based on body mass index (BMI), in obese (n = 9, BMI: mean 29.4 kg/m^2) and non-obese (n=6, BMI: mean 24.8 kg/m^2). A serial of blood samples was collected at the pre- and post-operative periods at time dosing interval (τ); propranolol plasma levels were measured one day before and after surgery using a high performance liquid chromatographic procedure described previously. PK Solutions software 2.0 was applied to obtain pharmacokinetic parameters. No changes on kinetic parameters as biological half-life ($t_{1/2}$, p = 0.0625, NS), volume of distribution (Vd/F, p=0.8438, NS) and plasma clearance (CL_T/F, p = 0.1563, NS) were obtained for the non-obese patients, while a prolongation of $t_{1/2}$ (3.2 to 11.2 h, p< 0.0039), an increase on Vd/F (3.0 to 7.7 L/kg, p<0.0039) and reduction on CL_T/F (11.3 to 9.2 mL/min.kg, p<0.0391) were obtained in the post-operative period for obese patients. Pharmacokinetic data could justify propranolol plasma concentrations in obese patients higher than in non-obeses, after surgery.

Uniterms
- Obesity
- Propranolol
- Pharmacokinetics
- Hypothermic cardiopulmonary bypass

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INTRODUCTION

Propranolol, a nonselective beta-adrenergic blocking agent, is an usual drug prescribed for treatment of arterial hypertension, angina pectoris, and cardiac arrhythmia. It is totally absorbed after the oral dose, shows a first-pass effect and consequently a low fraction of dose absorbed reaches the systemic circulation as unchanged drug. The drug highly distributed, also binds to plasma proteins, with approximately 90% of the circulating drug

bounded mainly to plasma α1-acid glycoprotein (Sager *et al*., 1989). Additionally, this lipophilic drug is extensively biotransformed by the liver, with most inactive metabolites excreted in the urine.

High variability in pharmacokinetics of propranolol reported in normal subjects and also in patients, affecting mainly distribution and elimination of drug (Jones *et al*., 1976; Boudoulas *et al*., 1978; McAllister *et al*., 1979; McAllister *et al*., 1980; Hoffman, Lefkowitz, 1996) associated to different response between individuals related to sympathetic tone (PDR, 1998) could explain the wide range on plasma levels noted at therapeutic doses required to reach clinical efficacy.

Propranolol plasma levels appear to be altered in surgical patients following coronary bypass grafting with mild hypothermic (~32 °C) cardiopulmonary bypass, CPB-H, (McAllister *et al*., 1979; Holley *et al*., 1982; Buylaert *et al.,* 1989). Consequently doses could be adjusted to avoid undesirable consequences in the post-operative period.

On the other hand, drug prescription for obese patients is not easy, since changes in dosage scheme, based on pharmacokinetic data in normal subjects, could induce errors (Cheymol *et al.,* 1997). Discussion remains, considering the influence of obesity on kinetics of propranolol reported previously and also the pharmacokinetic change after cardiopulmonary bypass in non-obese patients.

Then, a study protocol was designed to investigate the influence of CPB-H on the kinetic disposition of propranolol in obese patients with coronary heart disease indicated for myocardial revascularization with CPB under moderate hypothermia.

MATERIAL AND METHODS

Fifteen coronarian patients scheduled for myocardial revascularization with moderate hypothermic (~32 °C) cardiopulmonary bypass were included in the protocol. The Institutional Ethical Committee (N: 1414/98/109) previously approved this protocol, and all of the patients provided written informed consent to participate in the study. In addition, all procedures were performed in accordance with institutional guidelines. Ambulatorial patients (unstable angina) under chronic treatment receiving propranolol (10-40 mg PO two or three times a day, for several months) were included. They were distributed into two groups, obese patients (n = 9) and non-obese patients (n = 6), based on body mass index (BMI; reference for obesity >25 kg/m^2); additionally body weight deviation, expressed as percentage of ideal body weight (reference for obesity >10 %) was also compared to BMI for all patients.

Characteristics of subjects of both groups, expressed as the mean (CI 95), are as follows. Obese patients: age: 57 (52-63) yr; body weight: 83 (75-91) kg; height: 168 (161-174) cm; body mass index (BMI): 29.4 (27-32) kg/m$^{2;}$ body weight deviation: 29.2 (14-44)%; body surface area (BSA): 1.9 (1.8-2.0) m^2. Non-obese patients: age: 61 (56-65) yr; body weight: 71 (66-76) kg; height: 169 (164-173) cm; BMI: 24.8 (24-25) kg/m^2; body weight deviation: 3.1 (0.7-5.5) %; and BSA: 1.8 (1.7-1.9) m^2.

Selected coronary patients were in the infirmary for routine examination before surgery. A day before the surgical intervention, in the morning, after drug intake, pre-operative blood sampling was performed at time dose interval (zero, 2, 4, 6, and 8 h or 12 h) for pharmacokinetics. Then, early next morning, all patients were submitted to cardiac surgery with CPB - H. At the first post-operative day, they received propranolol PO dose, 10 mg once a day; blood samples were collected again at time dose interval (zero, 2, 4, 6, 8, 12 and 24 h) for pharmacokinetics.

Propranolol plasma levels were determined by high performance liquid chromatography with fluorescence detection (HPLC-F), as reported previously by Pereira *et al*. (2000). Twenty-five microliters of internal standard (verapamil 2.5 µg/assay), 200 µL of 1.25 N NaOH, and 3 mL of dichloromethane were added to 200 µL of plasma. Mixture was vortexed for 1 min and centrifuged for 30 min at 3000 rpm. Then, the organic phase was transferred and evaporated to dryness, and the residue was dissolved with 100 µL of mobile phase (0.38 M acetate buffer pH 5.0:acetonitrile 65:35, v/v) and injected into the HPLC system using analytical column (NovaPak C18 150 x 3.9 mm, 5 µm, Waters Assoc., Mildford, USA). Peaks were monitored using a fluorescence detector setted at 290 nm/358 nm, excitation/emission as described previously.

PK Solutions 2.0 software for pharmacokinetics was applied to data obtained. Area under the curve (AUC_T) and kinetic parameters obtained from plasma curve decay: apparent volume of distribution (Vd/F), and drug elimination measured through total body clearance (Cl_T/F), and biological half-life ($t_{1/2}$), at the pre-operative and post-operative periods were estimated.

The GraphPad InStat™ (GraphPad Software, San Diego, USA) was applied to the data obtained for statistics. Tests for paired and unpaired data were applied for statistical analysis and data reported in the present study was expressed as median, mean and CI95 range. Non parametric tests were applied and a significance $p < 0.05$ was considered.

RESULTS AND DISCUSSION

Pharmacokinetics of propranolol in obesity: non-obese *versus* obeses

At the pre-operative period, a slight but non significant reduction was obtained in plasma clearance and volume of distribution when obese patients were compared to the controls, remaining unchanged the biological half-life. Plasma levels comparing obese and non-obese patients in this period are showed in Figure 1.

Similar reductions in these parameters were reported previously for obese individuals *versus* normal subjects after IV single dose of propranolol (Cheymol *et al.,* 1987; Poirier *et al*., 1990; Cheymol *et al.,* 1997). The modification of regional blood flow was proposed by those authors to explain the altered tissue diffusion of drug in the obese subjects. Additionally, they reported that lipophilic beta-adrenoceptor blockers as propranolol seem to diffuse less into adipose than into lean tissues, based also on several electrical forms present (i.e. cations, neutral forms, or zwitterions) at physiological pH, that contribute to their tissue distribution in both obese and lean subjects. The tissue distribution in obese patients could be restricted by the sum of hydrophobic forces and hydrogen bonds they elicit with macromolecules in lean tissues (Cheymol *et al., 19*97).

According to Belfrage (1978), in a previous study carried out in dogs, changes in the vascular resistance of adipose tissues were induced by the activation of the sympathetic nerves and noradrenaline administration, as a consequence of the combined results of alpha-adrenergic vasoconstriction and beta-adrenergic vasodilatation. The author also reports that propranolol and practolol potentiate vasoconstriction induced by noradrenaline administration or sympathetic nerve stimulation in dogs.

Therefore, it is possible that a vasoconstriction by beta-blocking drugs in adipose tissue of humans could restrict the distribution of a highly lipid soluble substance such as propranolol without modifying the distribution of hydrophilic drugs as sotalol, because of its weak lipid solubility (Poirier *et al.*, 1990).

By the other hand, the plasma clearance of a substance with a high hepatic extraction ratio, such as propranolol, depends on hepatic blood flow rather than on the metabolic activity of liver in subjects with normal liver function (Weiss *et al.,* 1978). Additionally, as commented by Poirier *et al.*(1990), the decrease in total body plasma clearance of propranolol obtained by Braillon and Capron, (1983) as a consequence of histological hepatic alterations, could explain the reduction of metabolic capacity in obese subjects, in spite of routine liver function tests show to be unaltered in those subjects (Braillon *et al.,* 1985). Therefore, they proposed that these modifications could be due mainly to changes in tissue perfusion in obese individuals (Braillon, Capron, 1983; Braillon *et al.,* 1985)

Pharmacokinetics of propranolol in non-obese patients: post- *versus* pre-operative - influence of CPB-H

Pharmacokinetics of propranolol in non-obese patients remains unchanged after CPB-H as described in

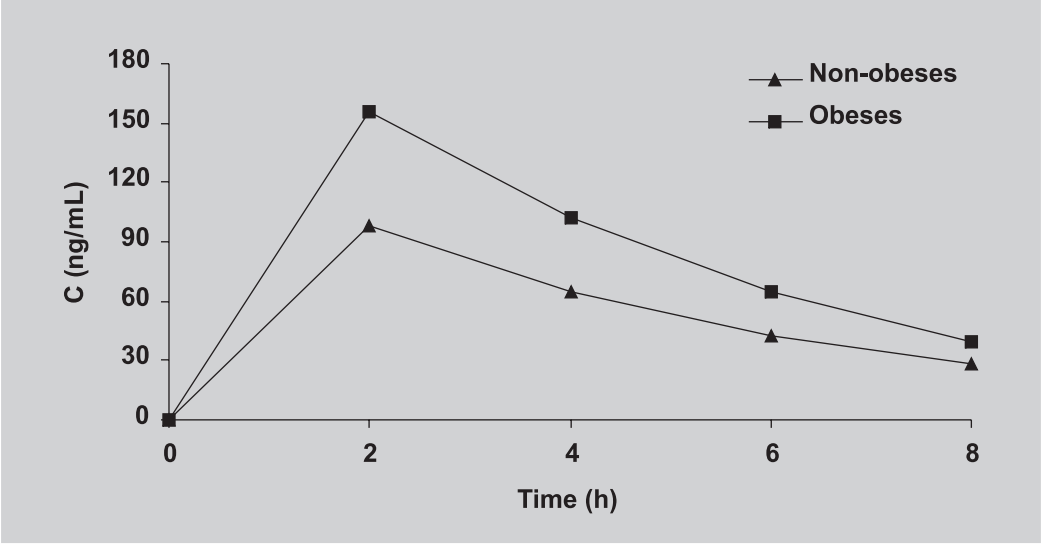

FIGURE 1 - Propranolol plasma levels (means) at the pre-operative period in patients: obeses, n = 9 *versus* non-obeses, n = 6.

Table 1. The high interindividual variation of plasma clearance, half-life and volume of distribution obtained in the present study showing non significant alterations, for non-obese patients after surgery could be supported by pharmacokinetic data reported previously for propranolol in healthy volunteers and also in patients after intravascular or peroral administration of single or chronic doses (Jones *et al*., 1976; Boudoulas *et al*., 1978, McAllister *et al*., 1979; McAllister *et al*., 1980; Hoffman, Lefkowitz, 1996; Cheymol *et al.,* 1997).

Obeses - influence of CPB-H

In parallel, at the first post-operative day, after the tracheal extubation and drug intake (propranolol PO dose, 10 mg once a day); significant alterations in the pharmacokinetics were obtained in obese patients, Table I. Plasma clearance was reduced from 11.3 mL/min.kg to 9.2 mL/min.kg, p = 0.0391), while volume of distribution was increased from 3.0 L/kg to 7.7 L/kg, (p = 0.0039); when periods before and after surgery were compared. Elimination half-life was prolonged by 3.5 fold (3.2 *vs* 11.2 h, p = 0.0039); then, it could be justified once non-proportional alterations were obtained in plasma clearance and volume of distribution after CPB-H.

Plasma drug concentration at dose interval in the post-operative period for both groups are illustrated in Figure 2.

It is well known that a 30% reduction of organ perfusion after cardiac surgery employing CPB can

TABLE I - Influence of CPB-H on pharmacokinetics of propranolol in obese patients

Kinetic Parameters (reference data 1*)	**Non-obese patients – CONTROL, median (CI95%) mean**		
	Pre-	**Post-**	**P**
$t_{1/2}$ (3.9+0.4 h)	3.1 (2.0-7.0) 4.5	7.6 (4.0-11.0) 7.5	0.0625
Cl_T/F (16+5 mL/min.kg)	17.2 (7.9-35.1) 21.5	9.0 (6.4-14.9) 10.7	0.1563
Vd/F (4.3+0.6 L/kg)	4.6 (1.1-13.9) 7.5	5.9 (3.0-10.9) 6.9	0.8438
	Obese patients - median (CI95%) mean		
$t_{1/2}$ (3.9+0.4 h)	3.2 (3.0-5.0) 4.0	11.2 (10.2-17.8) 14.0	0.0039
Cl_T/F (16+5 mL/min.kg)	11.3 (7.3-19.6) 13.4	9.2 (5.4-12.0) 8.7	0.0391
Vd/F (4.3+0.6 L/kg)	3.0 (1.3-9.4) 5.4	7.7 (5.2-15.9) 10.6	0.0039

Statistics: Wilcoxon's Test, post- *versus* pre-operative periods; significance level: p< 0.05; [1*] Reference values, Hardman J.G. *et al.* (1996).

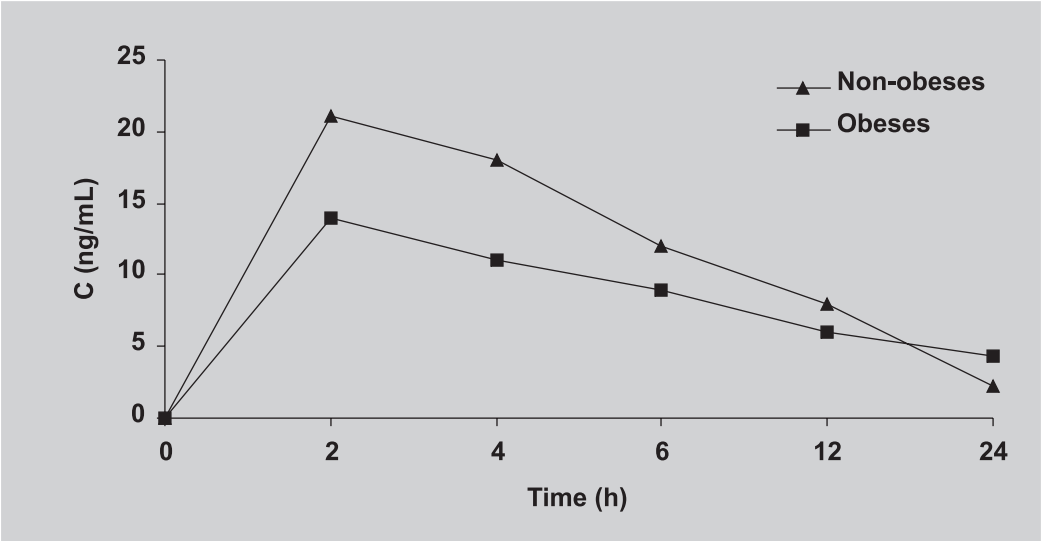

FIGURE 2 - Propranolol plasma levels (means) at the post-operative period in patients: obeses, n = 9 *versus* non-obeses, n = 6.

influence the elimination of drugs by the liver and kidneys, with kinetic consequences such as reduction on total body clearance and prolongation of elimination half-life (Babka, Pifarré, 1977; Fellander *et al*., 1996; Holley *et al*., 1982). In addition, drug distribution and its metabolism by the liver are altered by the systemic cooling during the hypothermic conditions decreasing volume of distribution and also plasma clearance as demonstrated in previous studies, (Babka, Pifarré, 1977; McAllister *et al.*, 1979; Fellander *et al*., 1996).

Therefore, in obese post surgical patients followed coronary bypass grafting with mild hypothermia (32 °C) associated to cardiopulmonary bypass, the pharmacokinetics of propranolol could be influenced by the increase of diffusion of the lipophilic beta blocking agent to tissues. These findings could be due to a lower restriction on the diffusion of this drug to the tissues in the obese subjects obtained after surgery, justifying the increase in volume of distribution and the prolongation of biological half-life.

It means that CPB-H could affect the equilibrium of several electrical forms present as a function of physiological pH after surgery contributing to their tissue distribution in a higher extension in obese than lean subjects investigated in the present study. Consequently, propranolol tissue distribution in obese patients could be restricted, before surgery, by the sum of hydrophobic forces and hydrogen bonds as reported previously by Cheymol *et al.*(1997). Changes obtained in drug distribution and elimination for obese patients after CPB-H suggest lower response to vasoconstriction induced by noradrenaline administration or sympathetic nerve stimulation potentiated by propranolol that could justify its influence on the pharmacokinetics in obese patients after surgery.

Data obtained indicate that CPB-H affects the pharmacokinetics of propranolol by increase of the extension of distribution and prolongation of biological half-life in obese patients, while plasma clearance was reduced in a lower extension. Pharmacokinetic data could justify propranolol plasma concentrations in obese patients higher than in non-obeses, after surgery.

RESUMO

Influência da obesidade na farmacocinética do propranolol em pacientes submetidos à revascularização do miocárdio com circulação extracorpórea

As concentrações plasmáticas e a disposição cinética do propranolol podem ser alteradas pela circulação extracorpórea (CEC). Investigou-se a influência da obesidade na farmacocinética do propranolol em pacientes submetidos à revascularização do miocárdio empregando a CEC. Investigaram-se quinze pacientes, recebendo cronicamente propranolol no pré- (10-40 mg, 2 a 3 vezes ao dia PO) e no pós-operatório (10 mg, 1 vez ao dia) sendo os mesmos distribuídos em dois grupos: obesos (n = 9, média 29,4) kg/m^2; e não-obesos (n = 6, média 24,8 kg/m^2). Colheram-se amostras seriadas de sangue nos períodos pré- e pós-operatório (τ); determinaram-se as concentrações plasmáticas do propranolol através da cromatografia líquida de alta eficiência. Aplicou-se o software PK Solutions 2.0 para estimativa dos parâmetros cinéticos. Não se registrou alteração na farmacocinética do propranolol avaliada através dos parâmetros meia-vida biológica ($t_{1/2}$), volume de distribuição aparente (Vd/F) e depuração plasmática (CL_T/F) no grupo de pacientes não-obesos, enquanto prolongamento relevante da $t_{1/2}$ (3,2 para 11,2 h, p<0,0039), aumento no Vd/F (3,0 para 7,7 L/kg, p < 0,0039) e redução no CL_T/F (11,3 para 9,2 mL/min.kg, p<0,0391) foram observados no grupo de pacientes obesos, no pós-operatório de revascularização do miocárdio empregando circulação extracorpórea e hipotermia. Os parâmetros farmacocinéticos obtidos poderiam justificar as concentrações plasmáticas do propranolol nos pacientes obesos superiores àquelas obtidas para não obesos após a cirurgia cardíaca.

UNITERMOS: Propranolol. Farmacocinética. Circulação extracorpórea. Obesidade.

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