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Cardiopulmonary bypass alters the pharmacokinetics of propranolol in patients undergoing cardiac surgery

M.J.C. Carmona[1], L.M.S. Malbouisson[1], V.A. Pereira[2], M.A. Bertoline[2], C.E.K. Omosako[2], K.B. Le Bihan[1], J.O.C. Auler Jr.[1] and S.R.C.J. Santos[2]

[1]Disciplina de Anestesiologia, Serviço de Anestesiologia e Terapia Intensiva Cirúrgica, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, and [2]Laboratório de Farmacologia Clínica, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP, Brasil

Abstract

The pharmacokinetics of propranolol may be altered by hypothermic cardiopulmonary bypass (CPB), resulting in unpredictable postoperative hemodynamic responses to usual doses. The objective of the present study was to investigate the pharmacokinetics of propranolol in patients undergoing coronary artery bypass grafting (CABG) by CPB under moderate hypothermia. We evaluated 11 patients, 4 women and 7 men (mean age 57 ± 8 years, mean weight 75.4 ± 11.9 kg and mean body surface area 1.83 ± 0.19 m^2), receiving propranolol before surgery (80-240 mg a day) and postoperatively (10 mg a day). Plasma propranolol levels were measured before and after CPB by high-performance liquid chromatography. Pharmacokinetic Solutions 2.0 software was used to estimate the pharmacokinetic parameters after administration of the drug pre- and postoperatively. There was an increase of biological half-life from 4.5 (95% CI = 3.9-6.9) to 10.6 h (95% CI = 8.2-14.7; $P < 0.01$) and an increase in volume of distribution from 4.9 (95% CI = 3.2-14.3) to 8.3 l/kg (95% CI = 6.5-32.1; $P < 0.05$), while total clearance remained unchanged 9.2 (95% CI = 7.7-24.6) *vs* 10.7 ml min^{-1} kg^{-1} (95% CI = 7.7-26.6; NS) after surgery. In conclusion, increases in drug distribution could be explained in part by hemodilution during CPB. On the other hand, the increase of biological half-life can be attributed to changes in hepatic metabolism induced by CPB under moderate hypothermia. These alterations in the pharmacokinetics of propranolol after CABG with hypothermic CPB might induce a greater myocardial depression in response to propranolol than would be expected with an equivalent dose during the postoperative period.

Correspondence
M.J.C. Carmona
Serviço de Anestesiologia e
Terapia Intensiva Cirúrgica
InCor, HC, FM, USP
Av. Dr. Eneas C. Aguiar, 44
2º andar
05403-000 São Paulo, SP
Brasil
Fax: +55-11-3082-2354
E-mail: maria.carmona@incor.usp.br

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Introduction

ß-adrenoreceptor antagonists improve acute outcomes and long-term prognosis in ischemic heart disease (1) and reduce perioperative events among high risk patients undergoing major non-cardiac and vascular surgery (2,3). Preoperative ß-blocker therapy has been shown to reduce the incidence of intraoperative ischemic events related to increases in heart rate (4,5) and hemodynamic responses to surgical stimulation during revascularization of the myocardium. Administration of a ß-blocker before coronary bypass and its immediate reinstitution afterwards is considered to be safe and beneficial (6,7), whereas an abrupt withdrawal of the drug has been associated with myocardial ischemia, hypertension, and tachydysrhythmias secondary to a ß-blockade-induced increase in ß-receptor density (8).

When patients undergoing coronary artery bypass graft (CABG) surgery receive propranolol preoperatively, it is assumed that propranolol should be reintroduced early in the postoperative period. However, clinical experience shows that the dose required to obtain adequate ß-blockade using propranolol in the immediate postoperative period is lower than that needed in the preoperative period. Some investigators have shown that hypothermia and cardiopulmonary bypass (CPB) can induce a change in plasma propranolol levels (9-11), but there are no studies analyzing the effects of hypothermic CPB on postoperative propranolol pharmacokinetics. The objective of the present study was to evaluate changes in postoperative propranolol pharmacokinetics in patients with coronary heart disease undergoing CABG with CPB under moderate hypothermia.

Patients and Methods

The study protocol was approved by the Hospital Ethics Committee, and written informed consent was obtained from all the patients included. Fourteen patients scheduled for CABG under moderate hypothermic CPB were enrolled into the study. Inclusion criteria were: a) left ventricular ejection fraction greater than 0.5 and normal right ventricular function assessed by preoperative transthoracic echocardiography in the week preceding the surgery; b) normal hepatic and renal function. We excluded patients with diabetes mellitus, chronic obstructive lung disease, peripheral arterial vascular disease, or submitted to off-pump CABG.

Monitoring, anesthetic and surgical procedures

Each patient received 0.1 to 0.2 mg/kg midazolam orally 30 min before surgery. After the patient was admitted into the surgical room, electrocardiographic monitoring configured to continuously display the DII and V5 leads and pulse oximetry were installed. Invasive arterial pressure monitoring was obtained by puncture of left radial artery using a specific 20-gauge radial catheter (Quickflash set; Arrow, Erding, Germany). Anesthesia was induced with 0.3 to 0.5 μg/kg sufentanil, 0.3 mg/kg midazolam and 0.1 to 0.2 mg/kg pancuronium bromide. Anesthesia was maintained by isoflurane inhalation and supplementary doses of sufentanil and pancuronium bromide. During CPB, hypnosis was maintained with supplementary doses of midazolam. For each patient, tidal volume was limited to 8 ml/kg and respiratory rate was set in order to achieve $PaCO_2$ values between 30 and 40 mmHg, without generating auto-positive end-expiratory pressure (auto-PEEP) (12). An inspiratory time of 33% and a FiO_2 of 0.60 were maintained throughout surgery. PEEP of 5 cmH_2O was implemented after intubation and maintained throughout surgery. After anesthetic induction, a fiberoptic ther-

modilution pulmonary artery catheter (CCO/SvO_2/VIP™TD catheter; Baxter Healthcare Co., Irvine, CA, USA) was inserted in all patients through the right internal jugular vein. An esophageal thermometer and a vesical catheter were also inserted after anesthetic induction.

After opening of the chest and dissection of the vascular structures, cannulas were inserted into the aorta and into the inferior and superior vena cava. CPB was performed using an extracorporeal circuit and membrane oxygenator primed with lactated Ringer solution. After initiation of CPB, patients were cooled and core temperature was maintained at 32º to 34ºC (89.6º to 93.2ºF) until the end of coronary grafting. After rewarming to 37ºC (98.6ºF), the patients were weaned from CPB. Vasoactive drugs were infused when judged necessary by the attending anesthesiologist.

Study protocol and propranolol measurements

All patients were chronically receiving oral propranolol (Inderal®; Astra-Zeneca, São Paulo, SP, Brazil), with total daily doses ranging from 80 to 240 mg. Immediately before the administration of the last preoperative dose of propranolol the night before surgery, a blood sample was collected to measure baseline plasma propranolol concentration. The patients then received 20 to 80 mg propranolol according to their standard dose regimen and other blood samples were drawn at 2, 4, 6, and 8 h for preoperative pharmacokinetic modeling. Patients underwent surgery the following morning. Eighteen hours after surgery, on the first postoperative day after the patients were allowed to drink water, a postoperative baseline blood sample was collected and 10 mg propranolol was administered *per os*. For postoperative pharmacokinetics, blood samples were collected at 2, 4, 6, 8, 12, and 24 h. EDTA tubes containing blood samples were centrifuged at 1500 *g* for 10 min and stored at a temperature of -70ºC (-158ºF) until the time for the drug assay.

The drug assay was performed using high-performance liquid chromatography (HPLC) with fluorescence detection as previously described by our group (13). Briefly, plasma propranolol concentration was determined by HPLC-F after a simple clean-up of plasma consisting of a single extraction, by adding 200 µl 1.25 N NaOH to a glass tube containing 200 µl plasma plus the internal standard (verapamil hydrochloride, 2.5 µg/assay). The mixture was vortexed for 1 min, followed by centrifugation at 1500 *g* for 10 min, and the methylene chloride phase was separated and immersed in a liquid nitrogen bath. The organic phase was transferred to a conic glass tube and dried to residue in a stream of nitrogen. The residue was then dissolved with 100 µl mobile phase and injected with a 20-µl loop into a Shimadzu LC-10A apparatus (Shimadzu Corp., Kyoto, Japan) connected to a 4-micron reverse phase 3.9 x 150 mm NovaPak™ C18 column (Waters Corp., Milford, MA, USA). The binary mobile phase consisting of 0.38 M acetate buffer, pH 5.0, and acetonitrile (65:35, v/v) was pumped isocratically at a flow rate of 0.7 ml/min. The peaks were monitored using a Shimadzu RF 10 AXL fluorescence detector at 290 nm (excitation) and 358 nm (emission). The Pharmacokinetic Solutions 2.0 software (Pharmacokinetics and Metabolism Software, Ashland, OH, USA) was applied to estimate the following major kinetic parameters: apparent volume of distribution, total body clearance and biological beta half-life.

Statistical analysis

Statistical analysis was performed using the SPSS 10 statistical package (SPSS Inc., Cary, CA, USA). The distribution of the data was visually evaluated by analysis of the distribution histogram and by the Kolmogorov-Smirnov test. If the distribution was consid-

ered to be not normal, a non-parametrical statistical test was applied. In order to evaluate the decay of plasma propranolol levels pre- and postoperatively, since propranolol loading doses were different at these times, linear regression models were fitted from plasma propranolol level decay with time. This permitted comparisons of the slopes of the equations obtained for 9 patients who received 40 mg propranolol preoperatively and all patients postoperatively. Pharmacokinetic parameters were compared before and after surgery by the Wilcoxon rank test. The correlation between percent variation of biological half-life and volume of distribution was determined by linear regression. Correlations between the length of CPB and pharmacokinetic parameters were determined by the Spearman rank test. A P value of <0.05 was considered to be statistically significant. All data are reported as means ± SD when they were normally distributed or as median ± 95% CI when the distribution was not normal.

Results

Fifteen patients were initially selected for the study but four of them underwent off-pump CABG and thus were excluded. The characteristics of the 11 patients enrolled are presented in Table 1. Mean age was 57 years (41 to 70 years) and the median preoperative risk estimate according to the criteria proposed by Higgins et al. (14) was 3, ranging from 0 to 6. The length of the surgical procedure was 420 ± 47 min and mean CPB duration was 107 ± 32 min. Dobutamine infusion at doses lower than 5.0 μg kg^{-1} min^{-1} was necessary for 2 patients during weaning from CPB. Nitroglycerine was administered after CPB to 10 patients and sodium nitroprusside to 7 patients. All patients achieved hemodynamic stability in the immediate postoperative period, which allowed weaning from vasoactive drugs within 24 h. Acute atrial fibrillation and bronchospasm were detected in two patients after discharge from the intensive care unit (ICU). The mean length of stay in the ICU was 48 h, ranging from 36 to 90 h, and mean hospitalization time was 6 days.

Figure 1 illustrates the decay of plasma propranolol levels with time for 9 patients who had received a loading dose of 40 mg propranolol in the preoperative period and in all patients in the postoperative period who received a single 10 mg dose. The shapes and slopes of the pre- and postoperative plasma propranolol decline curves were different. Linear regression analysis of the pre- and postoperative data

Table 1. Characteristics of the patients.

Patient No.	Age (years)	Gender	Weight (kg)	Height (cm)	BSA (m^2)	Last preoperative propranolol dose (mg)	Preoperative risk score	CPB length (min)	ICU stay (h)
1	63	F	88	160	1.95	40	4	75	46
2	67	M	80	170	1.90	40	6	135	50
3	56	F	67	160	1.70	40	1	105	65
4	58	F	70	165	1.80	40	0	145	41
5	58	M	90	179	2.10	40	0	100	44
6	60	M	59	158	1.60	40	2	115	42
7	48	M	73	168	1.85	40	0	160	36
8	57	M	60	160	1.62	20	3	73	39
9	49	M	70	160	1.70	40	3	100	90
10	70	F	78	150	1.70	80	5	50	43
11	41	M	95	174	2.20	40	3	120	41

F = female; M = male; BSA = body surface area; CPB = cardiopulmonary bypass; ICU = stay in intensive care unit. Preoperative risk score as proposed by Higgins et al. (14).

sets presented in Figure 1 indicated different slopes, -30.1 *vs* -2.1.

As can be seen in Table 2, after CABG with hypothermic CPB there was a mean increase of 6.1 h in the biological half-life of propranolol, which was 236% higher than the preoperative value. The same behavior was observed regarding distribution volume, which was 4.3 l/kg greater than the preoperative value, representing a 208% increase. A good correlation between distribution volume and half-life ($r^2 = 0.93$) was also observed, as illustrated in Figure 2.

On the other hand, no significant postoperative changes were observed in total body clearance of propranolol. No relationship was observed between the length of CPB or esophageal temperature during CPB and postoperative propranolol pharmacokinetic parameters (biological half-life, distribution volume and total body clearance) or between the percentual postoperative to preoperative variation in these parameters.

Discussion

In the present study, a decrease in the level of plasma propranolol clearance was observed in patients undergoing CABG surgery with hypothermic CPB compared to preoperative plasma clearance values. Analysis of the propranolol pharmacokinetics revealed a significant increase in the biological half-life and volume distribution of propranolol induced by CABG with hypothermic CPB on the first postoperative day. On the other hand, no alterations were observed in postoperative total body clearance of propranolol. No relationship was found between the length of CPB or temperature during CPB and biological half-life, distribution volume and total body clearance or between the percentual postoperative to preoperative variation in these parameters.

Methodological limitations

The patients selected for this study had low surgical risk, estimated using a standard cardiac surgical risk score system (14). Since at our institution most of low surgical risk patients are planned to undergo off-pump CABG surgery, only few patients for whom CPB was anticipated fulfilled the criteria for inclusion in the study, thereby limiting the sample size.

Although a 40-mg dose of propranolol

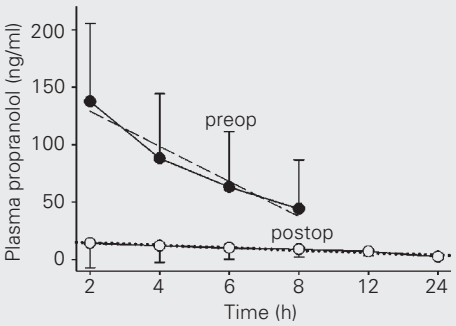

Figure 1. Plasma propranolol levels before and after coronary artery bypass grafting with hypothermic cardiopulmonary bypass. The filled circles indicate preoperative measurements and the open circles postoperative measurements. The dashed line shows the linear regression of preoperative plasma propranolol levels and the dotted line shows the linear regression of postoperative levels. Data are reported as median and 95% confidence interval for 9 patients preoperatively and 11 patients postoperatively. $Y_{preop} = 129 - 30.1x$; $R^2 = 0.95$. $Y_{postop} = 14.3 - 2.1x$; $R^2 = 0.95$.

Table 2. Pre- and postoperative propranolol pharmacokinetics determined in 11 patients.

Kinetic parameters (reference data)	Preoperative	Postoperative
$t_{1/2}$ (3.9 + 0.4 h)	4.5 (3.9-6.9)	10.6 (8.2-14.7)*
CL_T/F (16 ± 5 ml min^{-1} kg^{-1})	9.2 (7.7-24.6)	10.7 (7.7-26.6)
Vd/F (4.3 ± 0.6 l/kg)	4.9 (3.2-14.3)	8.3 (6.5-32.1)*

$t_{1/2}$ = biological half-life; CL_T/F = total body clearance; Vd/F = apparent volume of distribution. Data are reported as median values and 95% confidence interval, in parentheses, for 11 patients.
*P < 0.05 compared to preoperative parameters (Wilcoxon rank test).

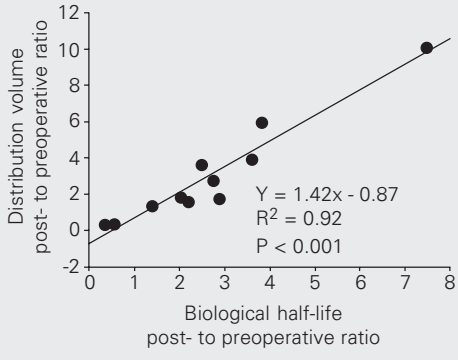

Figure 2. Correlation between the distribution volume postoperative:preoperative ratio and the postoperative:preoperative biological half-life ratio of propranolol.

was administered to most patients the night before surgery, 2 patients received loading doses of 20 and 80 mg, respectively. The patients included in the study were treated with propranolol regimens tailored by the attending cardiologists according to clinical parameters and individual tolerance. As a consequence, it was not possible to use a standard preoperative loading dose. It was therefore expected that the plasma propranolol levels of these two patients would differ from those of the other patients. For this reason, data from these two patients were not used in the regression model used to calculate the curves of plasma level decay. On the other hand, the patients included in the study presented normal preoperative plasma protein levels, hepatic and renal function, and theoretically, the different loading doses should not have interfered with the pharmacokinetic behavior of propranolol, being these two patients kept in the pharmacokinetical analysis.

Another factor that could cause concern about the methodology was that the activity of P450 cytochrome, the enzyme responsible for the metabolism of propranolol, was not evaluated in the present study. Thus, it was impossible to classify the patients as extensive or poor metabolizers according to hepatic hydroxylation velocity (15). Variable P450 cytochrome activity is known to occur naturally in humans and may be associated with differences in the pharmacokinetic profile of propranolol (16). Although the poor metabolizer phenotype is an autosomal Mendelian recessive character and the extensive metabolizer degree of dominance is estimated at 30% in the population, this selection bias was anticipated in the study design and paired statistical analysis was used to compare pharmacokinetics pre- and postoperatively.

An open monocompartmental model was applied to the study of propranolol pharmacokinetics. This model can only predict the elimination process by the monophasic decay of plasma propranolol level and estimate the other parameters such as biological half-life and distribution volume. This kind of model has been validated and used extensively to assess the pharmacokinetics of several drugs including propranolol (17-19). The metabolite 4-hydroxy-propranolol was not quantified due to the unavailability of an HPLC calibration standard. Although the ß-adrenergic blocking properties of propranolol are also due to this active metabolite, the metabolite does not influence propranolol pharmacokinetics.

Kinetics of propranolol distribution and coronary artery bypass graft surgery with hypothermic cardiopulmonary bypass

Propranolol, a nonselective ß-adrenoceptor blocking agent, is a lipophilic drug, almost totally absorbed after *per os* administration. It has an extensive first-pass effect and thus only a small percentage of active drug reaches the systemic circulation. Inter-individual variation in the pre-systemic elimination of the drug contributes to the wide range of plasma concentrations seen after oral dosing. Propranolol is a high extraction drug, extensively biotransformed by the liver, and most of its metabolites are excreted into urine. The biological half-life and plasma clearance of propranolol depend on hepatic blood flow, and thus they may change when co-administered with other drugs that affect propranolol metabolism and hepatic blood flow. The aromatic ring of the ß-blocker is responsible for the different lipophilicities of the drug molecules. Pharmacokinetically, this influences protein binding, hepatic extraction ratio and volume of distribution of most lipophilic ß-blockers, such as propranolol (20). Propranolol binds to plasma proteins, and approximately 90% of the circulating drug is bound mainly to plasma α_1-acid glycoprotein (21).

As expected, preoperative propranolol pharmacokinetics was essentially normal in

this study when compared to data reported by other investigators. Routledge and Schand (22) reported a biological half-life of 3.2 h (3-6 h), a steady-state volume of distribution ranging from 3 to 4 l/kg and a total body clearance ranging from 10 to 15 ml kg^{-1} min^{-1} in nonsurgical patients (22). Wojcicki and co-workers (19) observed a biological half-life of 5.2 ± 0.4 h in healthy volunteers. The distribution volume and total body clearance estimated in this study were within the same range of values described by Frishman and Alwarshetty (23).

CABG surgery with hypothermic CPB, on the other hand, induces profound alterations in propranolol pharmacokinetics. When extracorporeal circulatory assistance is started, a volume of 1500 to 2000 ml of crystalloid prime solution is acutely added to the blood volume, leading to a 40-50% decrease in plasma protein and a 50% decrease in the plasma levels of propranolol as a direct consequence of hemodilution (11,24). Lipid-soluble drugs with a high volume of distribution may be more readily taken up by bypass equipment, further contributing to a decrease in plasma levels. This initial fall in concentration at the start of CPB may be more readily counteracted by back diffusion into plasma if large tissue stores have accumulated (25). The decrease in plasma proteins also contributes to compensating the effect of CPB on plasma drug concentration by increasing the free fraction of drugs with a high plasma protein binding capacity, such as propranolol. Wood et al. (26) reported an increase in the free fraction of propranolol in plasma from 6.6 to 13.5% after institution of CPB. During hypothermia, microsomal enzyme and hepatic propranolol elimination is reduced, as well as the apparent distribution volume and total body clearance, resulting in plasma levels higher than predicted from kinetic patterns derived under normothermic conditions (9,10).

In the present study, a lower decline in plasma propranolol concentrations was observed on the first postoperative day when compared to the preoperative period. Plachetka et al. (11) reported a sustained increase in plasma propranolol levels that lasted for at least 4 h after CPB weaning. Although the results of Plachetka and co-workers pointed out early postoperative changes in propranolol pharmacokinetics, no studies were specifically addressed at the pharmacokinetic alterations occurring on the first postoperative day. A mean prolongation of the biological half-life of propranolol of 237% and a two-fold increase in propranolol distribution volume were detected. These postoperative changes in propranolol pharmacokinetics are probably multifactorial and some hypotheses may be raised to explain these changes. A post-CPB decrease in plasma protein concentration, mainly associated with a redistribution of propranolol from tissue stores to plasma, and the postoperative decrease in hepatic and renal function may be some relevant mechanisms.

The decrease in plasma proteins may persist after CPB and an increase in plasma free fraction of propranolol would be expected during the postoperative period. The initial decrease in the concentrations of α_1-acid glycoprotein was followed by a rise to 254% of baseline at 72 to 120 h, with approximately normal levels being observed on the first postoperative day. The free fraction of propranolol was also initially increased to 200% and fell progressively with time, reaching sustained troughs of 57% at 72 to 120 h (27). Since plasma protein levels increased toward normal values on the first postoperative day, these results argue in favor of alterations in propranolol protein binding properties contributing to propranolol pharmacokinetic alterations rather than to plasma protein dilution as a consequence of CPB hemodilution. On the other hand, we cannot assume that the effects of CPB on liver and renal function were the essential mechanisms involved in the changes observed in the pharmacokinetics of propranolol, since the

total body clearance was unchanged. Despite the absence of alteration in total body clearance, it is well known that CPB and hypothermia induce a 30% reduction in hepatic blood flow and influence the metabolism and elimination of the drug by the liver and kidney (28-30). Interindividual factors not taken into account in the present study might interfere with drug clearance after CPB, contributing to the wide variation observed pre- and postoperatively and possibly to the absence of difference. According to our data, no correlation was observed between the length of CPB or lowest CPB temperature and the changes in propranolol biological half-life, volume of distribution or total plasma clearance and there was a strong correlation between the increase in biological half-life and volume of distribution.

These major alterations in postoperative propranolol pharmacokinetics observed here could explain the decrease in the dose required for adequate ß-blockade effects. Considering the more extensive effect of hypothermic CPB on propranolol pharmacokinetics than on atenolol disposition (31), less lipophilic ß-blockers might be a better choice for pre- and postoperative treatment of patients undergoing CABG with CPB. The mechanisms explaining these alterations in propranolol pharmacokinetics on the first postoperative day are multiple and probably synergistic. More studies are necessary to elucidate the contribution of the individual mechanisms to the alterations observed.

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