Influence of Cardiopulmonary Bypass on the Plasma Concentrations of Atenolol

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Summary

Background: Betablockers are used in the treatment of angina pectoris and others ischemic coronary diseases, reducing mortality and cardiovascular events. Atenolol is a hydrophilic betablocker which is characterized by gastrointestinal absorption, small extent of distribution and renal function-dependent elimination.

Objective: The study objective was to determine the inter-individual variability of atenolol in coronary patients.

Methods: Plasma atenolol was quantified in six blood samples collected during the preoperative period from seven patients with coronary insufficiency and surgical indication, chronically treated with atenolol PO 25 to 100 mg/day. All patients presented a normal or slightly reduced renal function.

Results: All enrolled patients presented normal or slightly reduced renal function as a result of age and underlying disease. Atenolol plasma concentrations showed a monoexponential decline, confirming the first-order pharmacokinetics at the doses employed for the control of coronary insufficiency (mean ± SD): 123 ± 56, 329 ± 96, 288 ± 898, 258 ± 85, 228 ± 79 and 182 ± 73 ng/ml at times zero, 2, 4, 6, 8 and 12h after dose administration. The investigated group showed a small inter-patient variability of atenolol administrated at multiple regimens due to the hydrophilic characteristic of the drug. Furthermore, accumulation of atenolol administered chronically was greater in coronary patients, compared to healthy subjects.

Conclusion: In view of its cardio-selectivity and low-variability, atenolol should be used as the first-choice drug for the treatment of acute coronary syndrome and other cardiovascular diseases. (Arq Bras Cardiol 2007;88(6):562-567)

Key words: Atenolol, inter-patient variability, plasma concentration, coronary insufficiency.

Introduction

Cardiopulmonary bypass (CPB), used in most cardiac surgeries with cardioplegia, may cause important changes in the plasma concentrations and kinetics of many drugs and it could alter their therapeutic effects. During this procedure, many changes are introduced in the normal physiology of the patient, such as the institution of hypothermia, nonpulsatile blood flow, hemodilution and anticoagulation. Therefore, relevant hemodynamic changes occur in response to these important modifications caused by the redistribution of central blood flow, alterations in electrolytes and body fluids, and the release of endogenous substances due to surgical stress[1,2].

The individual characteristics of each drug are fundamental for the determination of the resulting plasma concentration. Lipophilic drugs with a large volume of distribution may be readily sequestered by the CPB equipment, with the abrupt fall in plasma concentrations at the beginning of CPB being reversed by return of the drug to the plasma[3]. In the case of the lipophilic betablocker propranolol, a 2.5 times prolongation of its biological half-life and a two-fold increase in its volume of distribution have been reported, in addition to the maintenance of high plasma concentrations immediately after myocardial revascularization with CPB and hypothermia. Thus, the propranolol dose administered during the postoperative period should be reduced when compared to the preoperative dose due to the risk of myocardial depression caused by the effect of the surgical procedure with CPB on the plasma concentrations and pharmacokinetics[4].

On the other hand, atenolol is a water-soluble and selective betablocker used pre-operatively for the control of angina pectoris, reducing the oxygen consumption[5], and to reduce the mortality and cardiovascular events after the surgical procedure[6-8]. With respect to its pharmacokinetic properties, atenolol is incompletely absorbed by the gastrointestinal tract (approximately 50%), has a relative small volume of distribution and renal function-dependent excretion[5,9].

Considering that there are no investigations available in the literature regarding the plasma levels of this hydrophilic betablocker under the influence of surgical procedure including CPB, the objective of the present study was to evaluate the effect of CPB on atenolol plasma concentrations, in order to determine

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if this drug could be safely reintroduced after the cardiac surgery, with or without the cardiopulmonary bypass.

Methods

Clinical protocol - The study protocol was approved by the Ethics Committees of the participating institutions. All patients included in the study signed the informed consent form after they had received detailed information about the procedures to be performed.

Nineteen adult patients of both sexes with coronary insufficiency, chronically treated with 25 to 100 mg of atenolol PO daily, and with surgical indication for myocardial revascularization, were investigated.

The patients, submitted to a coronary artery bypass graft surgery, were divided into two groups, denominated on-pump and off-pump groups, according to the surgeon indication or not for cardiopulmonary bypass use. The on-pump group consisted of 11 patients adults undergoing myocardial revascularization surgery with CPB, while the off-pump group consisted of 8 patients submitted to cardiac surgery without CPB.

Demographic characteristics of on-pump group, expressed as minimum and maximum values, are the following: 45-74 yrs (age), 62-118 kg (BW), 155-177 cm (height), 1.68-2.36 m^2 (BSA), 22.23-40.83 kg/m^2 (BMI). Demographic characteristics of patients enrolled in the off-pump group are summarized below: 54-69 yrs (age), 50-84 kg (BW), 147-175 cm (height), 1.49-1.98 m^2 (BSA), 19.78-30.12 kg/m^2 (BMI).

The patients included in both groups presented renal function within normal limits or mild renal failure as a result of underlying disease and age (patients ≥ 65 years). Enrolled patients also presented normal hepatic and endocrine functions. Excluded from the study were patients older than 80 years, patient with serum creatinine above 1.4 mg/dl, patients with a left ventricular ejection fraction less than 35%, patients with positive serology for hepatitis, nephrectomized patients, and patients with any contraindication for betablocker therapy.

On the day before surgery, the patients included in the study were submitted to routine preoperative physical and laboratory exams, and the surgical risk was also evaluated. After the initial assessment, the last dose of atenolol was administered on the day before the surgical procedure. Two blood samples (5 ml each) were collected through an arterial catheter on admission to the operating room and at the end of the intervention, from patients enrolled into both groups. For patients submitted to CPB, two additional blood samples were also collected at the beginning and at the end of the procedure.

During the surgical procedure, hematocrit, temperature and diuresis were also monitored. On the day after the surgical procedure, the patients were submitted to routine physical and laboratory exams, including the evaluation of renal function.

Analytical method - Atenolol was quantified in the collected samples by a micromethod using only 200 µL plasma. The samples were purified by plasma protein precipitation with acetonitrile followed by centrifugation at 6000 g; the organic extract was concentrated in a stream of nitrogen; residue was dissolved with 200mcL, transferred to inserts of vials and atenolol samples were determined by high-performance liquid chromatography with fluorescence detection using a C18 analytical column and a binary mobile phase at a low flow rate. Validation of this analytical method showed a good linear correlation (8 to 2000 ng/ml), high sensitivity (quantification limit: 8 ng/ml and detection limit: 4 ng/ml), accuracy of 99.3%, and intra and inter-day precision of 5.3 and 6.9%, respectively. Absolute recovery was 93.7% and the method was also found to be robust and with acceptable stability[10].

Statistical analysis - Plasma atenolol concentrations obtained during the intra-operative period were compared between the on-pump and off-pump groups by the Mann-Whitney test. On the other hand, plasma concentrations at the beginning versus at the end of surgery were analyzed in each group by the paired nonparametric Wilcoxon test. Finally, a nonparametric test for repeated measures (Friedman test) was used to analyze the plasma levels measured at the different sampling times in the on-pump group.

All statistical analyses were performed with the GraphPad Instat™ software (GraphPad Software Incorporated, San Diego, USA). The results are reported as median and upper and lower limit of the 95% confidence interval.

Results

The demographic data of the patients included in the two groups are summarized in Table 1.

Table 1 - Demographic characteristics of the patients investigated in the on-pump and off-pump groups, expressed as mean ± SD

Parameter	Unit	On-pump group	Off-pump group
Sex	F/M	M = 8 and F = 3	M = 5 and F = 3
Age	years	60.91 ± 7.49	60.88 ± 6.42
Weight	Kg	81.09 ± 15.13	66.38 ± 11.75
Height	m	1.70 ± 0.07	1.60 ± 0.08
Body mass index	kg/m^2	28.10 ± 4.91	25.87 ± 3.23
Body surface	m^2	1.95 ± 0.19	1.71 ± 0.18
Creatinine clearance	ml/min	83.85 ± 25.49	72.84 ± 20.87

Values are expressed as mean ± standard deviation. M – male; F – female.

All enrolled patients are being treated before the cardiac surgery with the hydrophilic betablocker atenolol in multiple dose regimens for the control of coronary insufficiency. The dose regimens used in both study groups were based on the clinical response of each patient, with each individual being treated with the lowest dose of the drug able to reduce the frequency and severity of ischemic attacks. In addition, the atenolol was suspended in the day before the cardiac revascularization in order to avoid cardiac depression. Therefore, the time interval between the administration of the last dose before the cardiac surgery and the beginning of the surgical procedure also differed among each investigated subject (table 2). However, the statistical analysis (Mann-Whitney test) showed that the two groups were comparable in terms of the preoperative atenolol dose (p=0.4421) and the time between the last dose and the beginning of revascularization surgery (p=0.7780).

In addition, it was also verified that both groups were comparable in terms of pre-operative renal function of investigated patients, since no statistical difference was observed between the two groups (creatinine clearance: p=0.3511). In addition, the renal function of the patients remained statistically unchanged when comparing the pre and postoperative periods in both groups of study (p > 0.05).

Figure 1 compares plasma atenolol concentrations, expressed in medians, measured during myocardial revascularization surgery for both studied groups (on-pump and off-pump groups). This figure also shows the plasma atenolol concentrations normalized for the preoperative dose administered. A more marked decrease in plasma atenolol concentrations was observed in patients undergoing cardiac surgery without CPB compared to the on-pump group. In addition, it was verified that the data obtained for the plasma atenolol concentrations normalized for the preoperative dose were similar to the obtained concentrations.

Table 2 - Descriptive data regarding the preoperative atenolol dose and interval between the administration of the last dose and the times of blood collection obtained for the on-pump and off-pump groups

Parameter	On-pump group	Off-pump group
Unit dose (mg)	50.00 (36.84 - 67.70)	50.00 (31.66 - 49.59)
Number of doses per day	1.00 (1.00 – 1.55)	1.00
Daily dose (mg)	50.00 (46.06 – 76.67)	50.00 (31.66 - 49.59)
Time interval between last dose and beginning of surgery (hours)	23.33 (16.15 – 25.02)	22.71 (18.77 - 25.00)
Time interval between last dose and end of surgery (hours)	28.75 (21.21 – 30.68)	26.25 (22.26 - 28.67)

Values are expressed as medians and upper and lower limit of the 95% confidence interval. * Mann-Whitney test, level of significance: p < 0.05.

Additionally, the descriptive results of the obtained plasma concentrations in both groups are presented in the table 3. The statistical analysis of plasma atenolol concentrations confirms that both groups are comparable at the beginning of the cardiac surgery (p=0.2375), since there is no statistic difference between the obtained concentrations. However, both groups presented distinctive behaviors during the intra-operative period, since at the end of the surgical procedure the plasma atenolol concentrations were statistically significant (p=0.0068).

Moreover, the patients submitted to the surgery with cardiopulmonary bypass present a less pronounced and non-significant decay in atenolol plasma levels (p=0.2754), when compared to the off-pump group (p=0.0156) due to the effects of CPB on the plasma concentrations of the drug.

Finally, as demonstrated in the table 4, no statistical difference was observed (Friedman test) for the plasma atenolol concentrations obtained for the on-pump group by comparison at the different sampling times (beginning of surgery, beginning of CPB, end of CPB and end of surgery).

Discussion

In the present study, the authors investigated the effects of CPB on the intraoperative concentrations of plasma atenolol during cardiac surgery in view of the lack of studies in the literature regarding these possible changes. Thus, the plasma levels of this betablocker were monitored during revascularization surgery with and without CPB (on-pump and off-pump groups, respectively).

In patients submitted to cardiac surgery with CPB, circulating atenolol levels tended to decrease (non-significantly) at the beginning of CPB as a result of hemodilution which occurs when the patient's blood is abruptly mixed with the perfusate during installation of CPB. This decrease was followed by a slight increase in plasma atenolol concentrations at the end of CPB (p > 0.05, NS), which can be explained by redistribution of the drug from the tissues to the central compartment which occurs to minimize the effects caused by hemodilution. No significant decrease in plasma atenolol levels was observed during the period from the end of CPB to the end of surgery due to continuous clearance of the drug from the organism through renal excretion.

When both groups were compared, the decay in plasma atenolol concentrations was found to be non-significant only in the on-pump group. This finding might be explained by the reduction in peripheral perfusion during CPB, with a consequent decrease in renal perfusion, and by the reduction in plasma clearance of the drug.

Another important factor during CPB is the isolation of the lungs from the circulation due to the interruption of pulmonary arterial flow. In this respect, the lung may function as a reservoir for basic lipophilic drugs such as propranolol and lidocaine which cannot be rapidly eliminated or distributed due to high protein binding. However, an increase in the plasma concentrations of these drugs has been reported to occur at

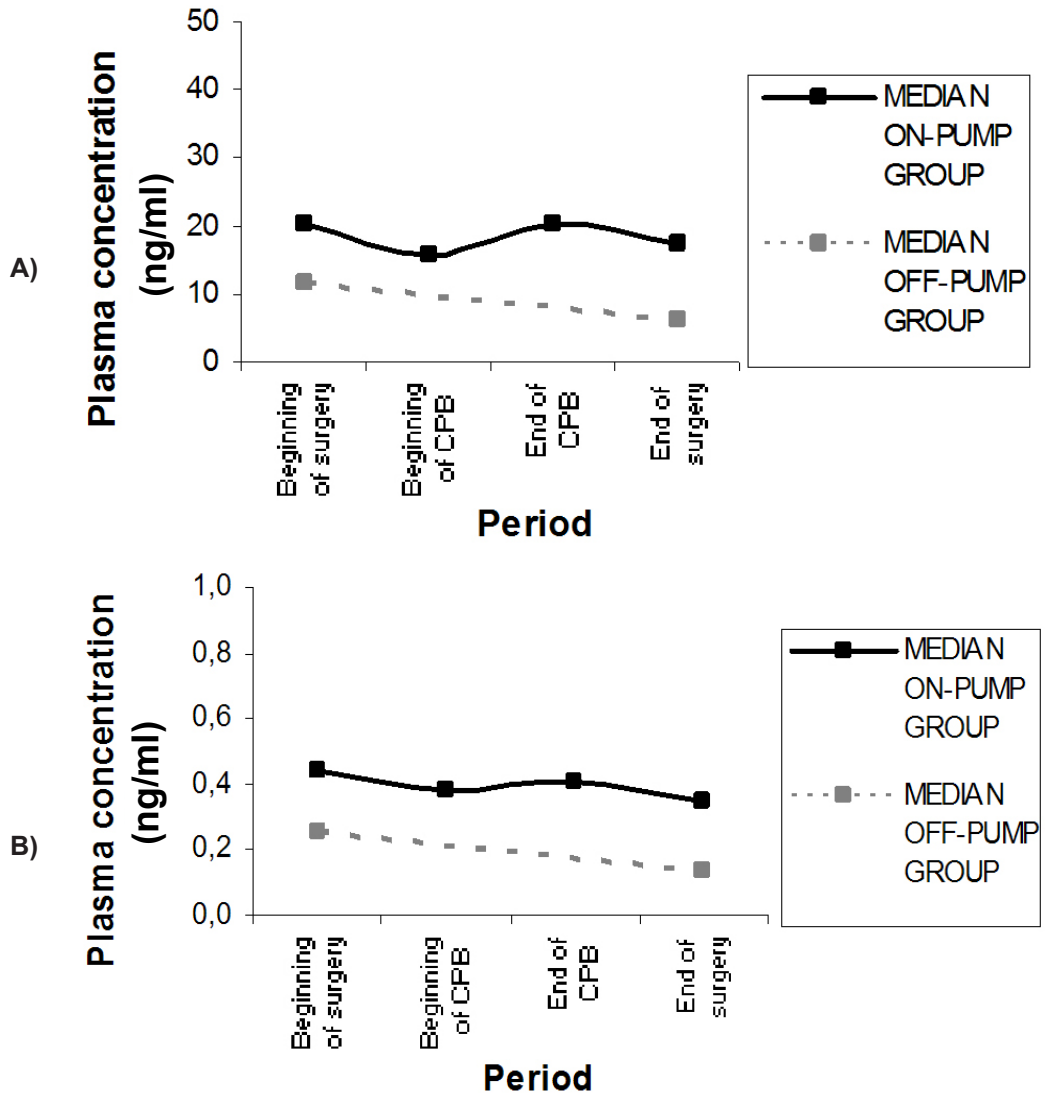

Fig. 1 - Intraoperative plasma atenolol concentrations obtained during cardiac surgery for the on-pump and off-pump groups. Values are expressed as medians. A) Plasma atenolol concentrations reported as ng/ml; B) Plasma concentrations corrected for the preoperative atenolol dose.

Table 3 - Statistical analysis of the plasma atenolol concentrations (ng/ml) obtained at the beginning and at the end of cardiac surgery for the on-pump and off-pump groups

Plasma concentration	On-pump group	Off-pump group	Statistical analysis * (on-pump versus off-pump)
Beginning of surgery	20.35 (11.22 – 36.29)	11.61 (4.84 – 26.51)	p = 0.2375 (NS)
End of surgery	17.29 (11.51 – 31.2)	6.02 (2.62 – 10.73)	p = 0.0068
Statistical analysis ** (beginning versus end of surgery)	p = 0.2754 (NS)	p = 0.0156	

Values are expressed as medians and upper and lower limit of the 95% confidence interval. * Mann-Whitney test, level of significance: $p < 0.05$. ** Wilcoxon test, level of significance: $p < 0.05$. NS - not significant.

Table 4 - Intraoperative plasma atenolol concentrations (ng/ml) obtained during cardiac surgery for patients of the on-pump group (n=11)

	Group 1	Group 2	Group 3	Group 4
	Beginning of surgery	Beginning of CPB	End of CPB	End of surgery
	20.35 (11.22 - 36.29)	15.76 (6.59 - 35.15)	20.35 (10.79 - 29.80)	17.29 (11.51 - 31.24)
Statistical analysis				
Group 1 x 2	p > 0.05 (NS)			
Group 1 x 3	p > 0.05 (NS)			
Group 1 x 4	p > 0.05 (NS)			
Group 2 x 3	p > 0.05 (NS)			
Group 2 x 4	p > 0.05 (NS)			

Values are expressed as medians and upper and lower limit of the 95% confidence interval. Friedman's nonparametric test for repeated measures, level of significance: $p < 0.05$.

the end of CPB due to re-establishment of the pulmonary circulation[2]. Thus, the higher plasma concentrations observed at the end of surgery in the on-pump group may also be explained by a possible return of atenolol deposited in the lungs to the circulation at the end of CPB. However, in the case of atenolol this effect is believed not to be very significant since the plasma protein binding of this hydrophilic molecule is low and its volume of distribution is relatively small.

Furthermore, when the on-pump and off-pump groups were compared in terms of plasma atenolol concentrations at the beginning versus the end of the revascularization, a significant difference was only observed between levels obtained at the end of surgery. This fact led us to conclude that plasma atenolol levels were comparable in the two groups at the beginning of cardiac surgery, but showed a significant difference at the end of the myocardium surgery due to the effects of CPB on the plasma concentrations of the drug, suggesting that CPB alters circulating atenolol levels during the surgical procedure.

With respect to the lipophilic betablocker propranolol, McAllister et al[11] observed a 50% reduction in plasma propranolol concentrations at the beginning of CPB. After the installation of CPB, the plasma levels of this drug remained unchanged or showed a slight increase during the CPB procedure. After the end of CPB and reheating of the patient, propranolol concentrations increased, reaching values similar to those observed at the beginning of surgery. According to these authors, plasma propranolol concentrations continued to be higher than those observed at the end of CPB up to 4 hours after CPB. The authors also suggested that hypothermia applied during CPB alters the distribution and plasma clearance of propranolol responsible for the marked increase in the plasma concentrations of this drug, which is counterbalanced by the effect of hemodilution[4,11]. In this respect, the literature reports that the propranolol dose necessary to achieve adequate betablockade during the postoperative period should be smaller than the dose administered before surgery[4].

The present results demonstrate that the behavior of atenolol differs from the lipophilic betablocker propranolol since no significant accumulation of the drug is observed at the end of cardiac surgery due to its hydrophilic characteristic, low plasma protein binding and relatively small apparent volume of distribution. Atenolol should therefore be adopted as the first-choice drug before and after surgery for the prevention of cardiovascular events resulting from surgical procedures performed with CPB. Furthermore, despite the renal function-dependent elimination of atenolol, the present results suggest that this hydrophilic betablocker can also be used safely in patients with slightly reduced renal function due to age and coronary insufficiency or even as a result of surgery.

Conclusion

On the basis of the present results, it is possible to suggest that the cardiac surgery with CPB causes changes in plasma atenolol concentrations without clinical relevance. Thus, despite the lower decline in plasma atenolol levels observed in patients submitted to CPB, this hydrophilic betablocker can be used safely in both groups since the surgical procedure, including CPB, does not lead to clinically relevant accumulation of the drug.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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