

Pharmacokinetic and Pharmacodynamic Evaluation of Atenolol during and after Pregnancy

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Study Objective. To evaluate changes due to pregnancy on atenolol's pharmacokinetics, response of maternal heart rate to atenolol, and the drug's effect on fetal heart rate.

Design. Prospective study.

Setting. Large university teaching hospital.

Patients. Fourteen pregnant women who were receiving oral atenolol for cardiac disease were enrolled and 10 completed the study.

Interventions. Patients were studied for 12 hours during the third trimester (TT) and again 6 weeks postpartum (PP).

Measurements and Main Results. Fetal heart rates, and maternal heart rates at rest and during exercise were recorded. Maternal plasma and urine atenolol concentrations were measured. Average resting heart rates (TT 68 ± 10 , PP 62 ± 9 beats/min) and maximum heart rate during exercise (TT 100 ± 6 , PP 87 ± 7 beats/min) were significantly higher in the third trimester than postpartum ($p < 0.05$). The 12-hour atenolol area under the curve (TT 0.208 ± 0.061 , PP 0.215 ± 0.089 ng/ml/day) and maximum plasma concentrations during the time of exercise tests (TT 1.07 ± 0.39 , PP 1.14 ± 0.53 mmol/L) were not significantly different. Individual and population pharmacokinetics did not differ significantly between study periods. The fetal heart rate did not correlate with maternal atenolol concentration.

Conclusion. Constant dosages of atenolol result in higher heart rates during pregnancy compared with the postpartum period. This lack of heart rate control is not due to significant changes in atenolol's pharmacokinetics or plasma concentrations.

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β -Blockers are widely administered during pregnancy to control heart rate in various conditions, including mitral stenosis, maternal and fetal supraventricular tachyarrhythmias, ischemic heart disease, and thyrotoxicosis.¹⁻³ Although anecdotal reports indicate potential side effects such as fetal growth retardation, bradycardia, hypoglycemia, hyperbilirubinemia, and apnea in the newborn,⁴ overall experience with the drugs in pregnancy has been favorable.³

Since nonselective β -blocking effects may increase uterine activity, β_1 -adrenergic receptor-blocking agents such as atenolol may be preferred during pregnancy.⁵⁻⁷

Our clinical experience suggested a need to increase the dosage of β -blockers to control heart rate during pregnancy. This observation, if correct, could be a result of a change in the pharmacokinetic behavior of the drugs in these women.

Due to physiologic changes occurring during pregnancy, profound and systematic changes in the pharmacokinetic behavior of drugs may occur.⁸ These changes have not been well studied in women receiving atenolol. Atenolol is a relatively hydrophilic drug with low protein binding (3%) that is eliminated renally.⁹ Its plasma half life is 4-10 hours in patients with normal renal function.^{10, 11} Ninety percent of the drug is recovered unchanged in urine.¹² Thus, renal clearance is a close estimate of total body clearance.^{13, 14}

In pregnancy, renal blood flow and glomerular filtration rate are greatly increased.¹⁵ Due to such changes, it seems reasonable to predict that atenolol's clearance may be higher and plasma half-life shorter, and that increases in weight and total body water may be associated with increases in volume of distribution. Changes such as these could lead to lower atenolol plasma concentrations. No longitudinal studies have evaluated the drug's pharmacokinetics in pregnant women, and little to no information is available regarding the relationship between maternal drug concentrations and effects on the fetus.

Methods

The study was designed to evaluate changes in the pharmacokinetics of atenolol during the third trimester of pregnancy and 6 weeks postpartum, compare maternal heart rate response at these two time periods, and evaluate the effect of maternal atenolol concentrations on fetal heart rate. The protocol was approved by the hospital institutional review board, and informed consent was obtained.

Patient Population

Subjects were pregnant women referred from the Los Angeles County-University of Southern California Medical Center's high-risk pregnancy clinic who required long-term oral atenolol for

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Table 1. Patient Characteristics

Variable	No.
Diagnosis	
Marfan's syndrome	1
Coarctation of the aorta	1
Mitral stenosis	4
Paroxysmal supraventricular tachycardia	7
Essential hypertension	1
Age (yrs)	30 ± 6
Weight during pregnancy (kg)	71.3 ± 12.1
Days of therapy before delivery	8-120

the management of cardiac disorders (Table 1). Exclusion criteria were age less than 18 years; hemoglobin below 10 g; serum creatinine greater than 2 mg/dl; left ventricular dysfunction; history of congestive heart failure, diabetes mellitus, or asthma; and concurrent therapy with other agents. Fourteen women were enrolled and completed the first part of the study. Four were lost to follow-up and did not return for the postpartum study.

Study Protocol

Of the 10 women who completed the entire study, 9 received atenolol 50 mg orally at 9 A.M. and 9 P.M. The last patient received 100 mg twice/day; her dosage was decreased to 50 mg every 12 hours 2 days before each study period so that it would be the same as that of the other patients. The duration of atenolol therapy before the gestational phase was at least 4 days, and patients continued long-term therapy throughout the postpartum period.

The women were admitted to the clinical research center the evening before the study day and received the 9 P.M. atenolol dose there. They were studied for 12 hours (one dosing interval) beginning at 9 A.M. when the morning dose was administered. The protocol was identical during both study periods (third trimester, approximately 6 wks postpartum).

Laboratory Data Collection

The following data were obtained for all patients during each study period: plasma atenolol concentrations immediately before and 1, 2, 3, 4, 6, 8, and 12 hours after the morning dose; and 12-hour urine collection started at 9 A.M. and collected in 3-hour increments to determine atenolol and creatinine levels. Plasma and urine samples were frozen at -70°C until analysis. Standard chemistry and hematology panels were performed.

Clinical Data Collection

Bioimpedance was measured to determine total body water,¹⁶ and a 12-lead electrocardiogram was performed. Every 3 hours resting heart rate was recorded, and resting blood pressure was measured by standard cuff method. During the third trimester the fetal heart rate was recorded for 10 minutes every 3 hours with a Hewlett Packard 8030A Cardiotocograph. Treadmill exercise following a modified Naughton protocol for 6 minutes¹⁷ was performed immediately before and 3 hours after the morning dose, with heart rate measured every minute. Exercise was contraindicated in one woman with Marfan's syndrome and ascending aortic aneurysm.¹⁸ Maternal blood and cord samples were obtained at delivery.

Atenolol Assay

Concentrations of atenolol in plasma and urine were determined by high-performance liquid chromatography (HPLC) with fluorescence detection.^{19,20} After addition of salbutamol as the internal standard, samples, controls, and standards were extracted by passing them through a C-18 solid extraction column. The extracts were dried and reconstituted in water and then injected into the HPLC and separated on a C-18 analytical column using ammonium phosphate buffer-acetonitrile as the mobile phase. The fluorescence detector was set at an excitation wavelength of 272 nm and emission wavelength of 606 nm. Each run of samples included a plasma standard curve covering the range of zero–5.6 mmol/L (1500 ng/ml) and three plasma controls with known atenolol concentrations at 0.2, 2.3, and 4.5 mmol/L (50, 600, 1200 ng/ml). The plasma and urine of each patient were extracted and run as a set along with standards and controls. Samples were analyzed in duplicate. The peak height ratio was used to calculate the concentrations.

Pharmacokinetic Analysis

To determine changes in pharmacokinetic values, each patient's data from the two time periods were evaluated. Individual pharmacokinetic values for both periods were determined by fitting a one-compartment model to the eight plasma levels from each study period using a weighted, nonlinear least squares regression analysis program (PC-Adapt) on a personal computer (Compaq 386). The program uses the

entire dosing, concentration in plasma, and estimated creatinine clearance histories.²¹ Concentrations in plasma were weighted by reciprocal of the variance of the assay.

Once individual values were obtained, the area under the concentration-time curve (AUC) was calculated with a clinical computer program (MB, USC*PACK PC collection, University of Southern California)²² that uses a method of discrete summation of concentrations in plasma. The program sums simulated concentrations in serum every 0.1 hour. Results of these analyses are analyzed for significant changes.

It was necessary to characterize the standard deviation of all possible atenolol concentrations so that it could be incorporated into the nonlinear fitting procedure. Therefore, standard deviations of control plasmas were fitted to a polynomial equation that described the overall relationship of the concentrations and their standard deviations.

A second analysis was done to build a population model to define the pharmacokinetic behavior of atenolol for the group as a whole during and after pregnancy. This analysis was performed on plasma levels to determine one-compartment mean and standard deviation population values with an iterative Bayesian computer method.²³ This analysis is similar to that described above, except that data from all 10 patients from each time period were evaluated together as a whole, creating a priori (Bayesian) population values that are incorporated into the fitting procedure.

To summarize, a Bayesian fitting procedure was performed on each patient datum separately during each iteration, producing values that are a result of both a priori values and the specific patient's data. Mean and standard deviation of the group were derived for each iteration; these then became a priori population values for the next iteration. Iterations continued in this way until predetermined convergence criteria were met. The resulting pharmacokinetic values for the third trimester and postpartum period were compared for significant differences.

To estimate bioavailability, all urine was collected during the 12-hour study period and atenolol concentrations were measured. The total amount of atenolol excreted in urine was equal to bioavailable atenolol.

Statistical Methods

The paired sample *t* test was used to test for

Table 2. Maximum Heart Rates and Atenolol Concentrations During Exercise

	Zero Hour ^a		3 Hours ^b	
	Third Trimester	Postpartum	Third Trimester	Postpartum
Heart rate (beats/min)	108 ± 15	91 ± 11 ^c	100 ± 6	87 ± 7 ^c
Atenolol plasma concentration				
mmol/L	0.41 ± 0.18	0.44 ± 0.30	1.07 ± 0.39	1.14 ± 0.53
ng/ml	109 ± 47	116 ± 79	286 ± 105	304 ± 142

^aTime of minimum concentration.

^bTime of maximum concentration.

^cp<0.05 comparing the third trimester and postpartum periods.

significant changes between the third trimester and postpartum in pharmacokinetic values and in resting and exercised heart rates. Population parameters were analyzed for significant differences using the Wilcoxon rank sum test. Significance was set at α of 0.05 and $1-\beta$ of 0.8.

Results

Patients were enrolled over 2 years.

Clinical Results

Heart Rate Control

All patients were in sinus rhythm. Average resting heart rates during the two 12-hour periods were significantly different, 68 ± 10 beats/minute in the third trimester and 62 ± 9 beats/minute postpartum (p<0.05). Changes at zero, 3, 9, and 12 hours were significantly different between study periods (Figure 1).

The maximum heart rate achieved by each patient during exercise was significantly lower at 3 hours after administration of atenolol (time 3) than immediately before the dose (time zero). Maximum heart rates during exercise at both

lowest and highest atenolol concentrations were significantly higher in the third trimester than in the postpartum (Table 2). The net increase during exercise at time zero and time 3 did not differ between periods (21 ± 8 and 20 ± 12 beats/min, respectively, NS).

Mean plasma atenolol concentrations measured at time zero and time 3 were similar between the third trimester and postpartum.

Fetal Heart Rates

Data from 13 patients were evaluable. Individual fetal heart rates remained relatively constant throughout the dosing interval and averaged 131 ± 8 beats/minute. Maximum maternal atenolol concentrations were not associated with consistent changes in fetal heart rate. Heart rate decreased slightly in six fetuses and increased or showed no change in seven during the 12-hour observation. In four fetuses heart rates were 120 beats/minute or below at some time during the dosing interval. They did not correlate with high maternal drug concentrations. In addition, maternal heart rates of 60 beats/minute or below were not associated with fetal heart rate 120 beats/minute or lower except in one case.

Delivery Concentrations

Data from nine patients were available at delivery. The average maternal blood:cord concentration ratio was 1.32 ± 1.1 (Table 3). The length of atenolol therapy before delivery ranged between 8 and 120 days.

Pharmacokinetic Results

The overall time to peak concentration for the whole group for both study periods was 3 hours after the dose, although most patients achieved near-peak concentrations at 1 hour. As shown in the Figure 2, concentrations remained near maximum for about 3 hours. The AUC for each

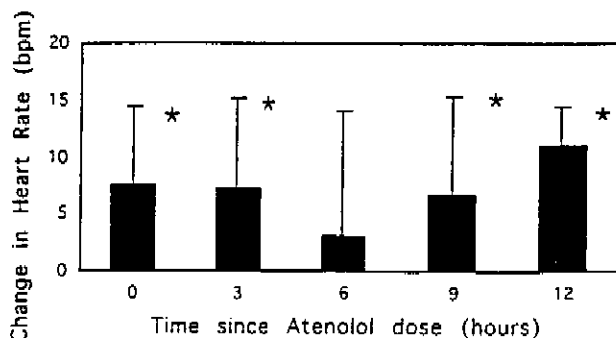


Figure 1. Changes in resting heart rate between the third trimester and postpartum (defined as heart rate in the third trimester minus heart rate in the postpartum period). Bars = 1 SD; * = p<0.05.

Table 3. Maternal and Cord Concentrations at Delivery from Nine Patients

Hours from Last Dose	Mother (ng/ml)	Cord (ng/ml)	M:C Ratio ^a
11	48	105	0.46
21	106	88	1.20
6	112	202	0.55
8	410	111	3.69
12 ^c	27	32	0.84
23	106	88	1.20
7	175	119	1.47
10	81	192	0.42
NA	NA	201	NA

NA = not available.

^aM:C ratio = maternal concentration divided by cord concentration.

patient and for the whole group did not differ significantly during the two time periods. Mean AUCs were 0.208 ± 0.061 ng/ml/day for the third trimester 0.0215 ± 0.089 ng/ml/day postpartum.

The interday assay error over a concentration range of 50–1500 ng/ml is described by the equation: $\text{ng/ml} = 25 - 0.046X + 0.00008X^2$. The coefficient of variation at the lower end of the range was approximately 15% and at 250 ng/ml it was 7%. Between 500 and 1500 ng/ml it was approximately 4%. This error pattern was incorporated into the pharmacokinetic modeling.

Table 4 shows individual patient pharmacokinetic values, determined from the weighted nonlinear least-squares regression analysis for the 10 women who completed both parts of the study. Changes in values between time periods were not significantly different, even though notable changes in parameters were seen in individual patients.

Body weight, total body water, and creatinine clearance were significantly higher during pregnancy, as expected. Respective mean values for the third trimester and postpartum were weight 74.5 ± 12.4 and 69.3 ± 11.8 kg, creatinine clearance 119 ± 23 and 97 ± 26 ml/min/1.73m², and total body water 34.4 ± 2.9 and 32.5 ± 3.3 L. Changes in total body water correlated with changes in weight but not with volume of distribution.

When comparing absorption rate constants between periods, large changes were observed in half of the patients. In three women they were greater than 5-fold. Overall, the value increased in six women in the postpartum period, remained constant in one, and decreased in three. This resulted in a higher mean postpartum values, but differences did not reach statistical significance due to large individual variations.

No significant differences were observed between third trimester and postpartum population values (Table 5).

Discussion

The heart rate was significantly higher, both at rest and during exercise, in women receiving identical dosages of atenolol, during the third trimester of pregnancy compared with the postpartum period. However, the study failed to find consistent change in atenolol pharmacokinetics during pregnancy and therefore excluded alteration in atenolol disposition as a cause for the higher heart rate during pregnancy.

Since the drug is renally excreted and relatively hydrophilic, it was expected that its clearance and volume of distribution would be higher during pregnancy. This was not found. Perhaps individual variations that occur during pregnancy are relatively small compared with overall normalcy of these patients with respect to their youth and otherwise good health (excellent nutrition status, renal function), aside from their cardiac disorder.

A limitation of the study was its small size. Analysis of power to detect changes in values indicates that in this group of 10 patients the magnitude of detectable differences is between 20% and 25%. To detect smaller differences, more patients are necessary. However, large numbers of pregnant women are usually not available for study, since drug therapy is avoided except when there is significant risk of serious

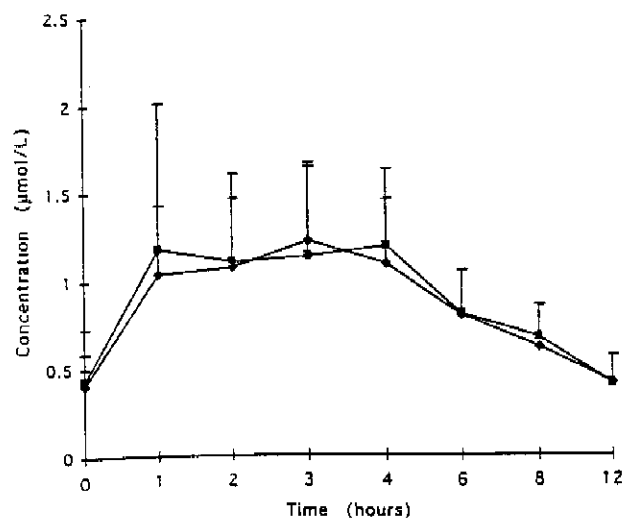


Figure 2. Average atenolol concentrations versus time. ♦ = average concentrations in the third trimester; ■ = average concentrations in the postpartum period; bars = 1 SD.

Table 4. Patient Pharmacokinetic Parameters

V (L/kg)		k _{el} (hr ⁻¹)		t _{1/2} (hrs)		Cl (L/kg/hr)		k _a (hr ⁻¹)		F	
TT	PP	TT	PP	TT	PP	TT	PP	TT	PP	TT	PP
0.84	0.95	0.106	0.095	6.5	7.3	0.089	0.090	0.581	0.732	0.28	0.47
0.51	0.64	0.186	0.301	3.7	2.3	0.096	0.191	0.313	0.300	0.28	0.49
0.54	0.48	0.223	0.254	3.1	2.7	0.121	0.121	0.816	0.254	0.54	0.40
1.11	0.63	0.102	0.143	6.8	4.8	0.113	0.090	6.483	1.551		0.33
0.78	0.93	0.150	0.127	4.6	5.4	0.118	0.131	1.307	12.633		0.23
1.06	1.03	0.097	0.143	7.2	4.9	0.102	0.147	1.943	0.394	0.32	0.39
0.39	0.31	0.121	0.136	5.7	5.1	0.048	0.042	0.512	0.758	0.36	0.36
0.67	0.69	0.176	0.152	3.9	4.6	0.118	0.104	1.207	1.478	0.49	0.44
0.94	0.72	0.072	0.112	9.6	6.2	0.068	0.80	0.852	0.540	0.27	0.17
0.69	0.76	0.251	0.177	2.8	3.9	0.174	0.153	0.253	11.541	0.61	0.66

TT = third trimester; PP = postpartum; V = volume of distribution; k_{el} = elimination rate constant; t_{1/2} = half-life; Cl = clearance; k_a = absorption rate constant; F = bioavailability.

Table 5. Population Model Parameters

	Third Trimester	Postpartum
V (L/kg)	0.72 ± 0.14	0.64 ± 0.15
k _{el} (hr ⁻¹)	0.16 ± 0.06	0.18 ± 0.05
Half-life (hrs)	5.0 ± 1.8	4.2 ± 1.0
Cl (L/kg/hr)	0.11 ± 0.04	0.11 ± 0.04
k _a (hr ⁻¹)	0.76 ± 0.40	0.87 ± 0.65

Cl = clearance; k_a = absorption rate constant; k_{el} = elimination rate constant; V = volume of distribution.

P values were not significant for differences between third trimester and postpartum parameters.

maternal morbidity and mortality. The pharmacokinetic findings in this report are supported by an earlier study that also failed to find a change in pharmacokinetics of atenolol during pregnancy when compared with nonpregnant women.²⁴ That study, however, did not have a longitudinal design and patients did not serve as their own controls. We believe that by having patients be their own controls we enhanced our ability to detect a difference.

It is possible to describe drug behavior in both individuals and in groups of patients. In this study we did both. The first assessment, which was nonlinear regression analysis, was used to arrive at individual values so that each woman's pharmacokinetic patterns could be evaluated for changes. The objective was to compare atenolol's pharmacokinetics during the third trimester with that when the patient was essentially back to normal 6 weeks after delivery. The other objective was to create population models for both time periods that could later be used when predicting values in other individuals. Population models describe central tendencies as well as expected variations. The iterative process used in this analysis, which incorporated all 10 patients' data at once when fitting parameters to

the data, resulted in values specific to the group, including variance and covariance. These values can be incorporated into software programs using standard Bayesian weighted nonlinear analysis, and dosage regimens may be revised in new patients with only limited clinical data.

Atenolol plasma concentrations during and after pregnancy were similar. Concentrations greater than 0.26 mmol/L (70 ng/ml) exert a significant effect on the heart rate.¹⁰ The minimum concentrations were above 0.26 mmol/L in all but three women in the third trimester and in all but two postpartum. Thus in most patients they were in the effective range throughout the dosing interval. The cause for the relative tachycardia in women receiving β -blocking therapy during pregnancy remains unclear, and may be related to physiologic acceleration in heart rate in pregnancy.

Increased sympathetic activity during pregnancy was proposed as an explanation for the increase in the frequency of arrhythmias and could explain the heart rate differences in the present study. This mechanism is not supported by catecholamine levels, however, which were reported to be either the same or lower in pregnancy compared with nonpregnant women.²⁵⁻²⁷ Increased responsiveness to what seem to be normal levels of circulating catecholamines during pregnancy may be an alternative, as yet uninvestigated, mechanism for the heart rate increase in our patients.

The fetal response to atenolol is hard to predict based on maternal concentrations and maternal heart rates. In studies of other β -blockers on neonates, overall fetal well-being correlated with the effect of the drug. Stressed newborns were more likely to exhibit adverse effects such as bradycardia, and it is possible that during stress

the fetus is more dependent on the β -adrenergic response, which is blocked by atenolol.²⁸

In conclusion, we found no consistent change in pharmacokinetics of atenolol during pregnancy, and if the same dosages are administered during pregnancy as in the nonpregnant state, heart rate will not be as well controlled. Failure to find altered atenolol pharmacokinetics during pregnancy, and findings of similar atenolol serum concentrations during the two phases of the study, exclude change in atenolol's disposition as a cause for higher heart rates during gestation.

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