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Atenolol Exposure and Risk for Development of Adverse Metabolic Effects: A Pilot Study

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Abstract

Study Objective—To evaluate whether the level of systemic exposure to atenolol explains observed interindividual differences in adverse metabolic responses.

Design—Open-label, prospective, pharmacokinetic pilot substudy of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study.

Setting—General clinical research center.

Patients—Fifteen hypertensive adults (mean age 46 ± 8.9 yrs) who were enrolled in the PEAR study.

Intervention—Patients received atenolol therapy for at least 8 weeks, with 5 of those weeks at a dosage of 100 mg/day, and then underwent a 2-hour oral glucose tolerance test during a pharmacokinetic study visit.

Measurements and Main Results—Twenty-hour plasma atenolol concentrations were measured during the pharmacokinetic visit. Glucose and insulin levels were measured during the 2-hour oral glucose tolerance test, and fasting plasma lipid, glucose, and insulin levels were measured at baseline and after 8 weeks of atenolol treatment. A significant association was noted between atenolol area under the concentration-time curve (AUC) and change in fasting glucose level when adjusted for covariates ($p=0.0025$); the effect was strongest in women. No significant relationship was noted between plasma atenolol concentration and glucose AUC during oral glucose tolerance testing ($r=0.08$, $p=0.78$), nor between atenolol AUC and change in triglyceride levels ($r=0.13$, $p=0.63$).

Conclusion—Higher plasma atenolol exposure may be a risk factor for an increase in fasting plasma glucose level during atenolol treatment. These findings require confirmation in a larger sample.

Keywords

hypertension; β -blockers; atenolol; adverse metabolic effect; oral glucose tolerance test; OGTT; plasma lipid levels; glucose

β -Blockers are recommended in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as acceptable first-line therapy for hypertension and are widely used for treating hypertension because of their safety and efficacy in reducing mortality and morbidity.¹ However, there have been recent concerns with the use of β -blockers as first-line therapy in hypertension, in part due to the increased risk for development of adverse metabolic effects on glucose, insulin, and lipid levels. Although there is little doubt about the benefit of β -blockers in patients with heart failure or those who have had a myocardial infarction, including when these patients also have diabetes mellitus, the data are less clear on the benefits of β -blockers in patients with uncomplicated hypertension. In these latter patients, the adverse metabolic effects are possibly of greater concern and have greater potential to offset benefits than in the other patient groups for whom the benefits of β -blockers are substantial.

Atenolol is a selective β_1 -adrenergic receptor blocker, widely used for the treatment of hypertension.^{2, 3} An association between atenolol use and adverse metabolic effects has been documented, but, to our knowledge, no studies have addressed the relationship between atenolol plasma concentrations and the occurrence of drug-induced changes in fasting glucose and triglyceride levels.^{4–11} Significant variability in the pharmacokinetics of atenolol could influence the development of the adverse metabolic effects that occur in only a fraction of the population exposed.^{12–14} This suggests that there are factors that predispose certain individuals to develop the atenolol-associated adverse metabolic effects. We hypothesized that occurrence of atenolol-associated metabolic abnormalities are concentration related and that people with higher plasma atenolol exposure are more likely to develop adverse metabolic effects. Therefore, we conducted a 24-hour pharmacokinetic study in adult hypertensive patients who were treated with atenolol for 8 weeks with dosage titration to 100 mg/day.

Methods

Study Patients

This was a prospective, open-label study in patients with hypertension who were aged 18–65 years, of any race, ethnicity, and sex, and who were enrolled in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study. The PEAR study is an ongoing hypertension pharmacogenomics study of the β -blocker atenolol and the diuretic hydrochlorothiazide given as monotherapy or in combination to determine which genes are associated with either antihypertensive response or adverse metabolic effects.¹⁵ The study began in January 2005 and is enrolling patients in Gainesville, Florida; Atlanta, Georgia; and Rochester, Minnesota. The trial is expected to be completed in 2010. Patients were required to have average home diastolic blood pressure greater than 85 mm Hg and office diastolic blood pressure greater than 90 mm Hg. The major exclusion criteria of the PEAR study were as follows: office or average home diastolic blood pressure greater than 110 mm Hg, office or average systolic blood pressure greater than 180 mm Hg, secondary form of hypertension, treatment with three or more antihypertensive agents, known cardiovascular disease, diabetes mellitus (type 1 or 2) or screening fasting blood glucose level above 126 mg/dl, serum creatinine concentration above 1.5 mg/dl in men and 1.4 mg/dl in women, primary renal disease, and pregnancy or lactation. Any patients receiving treatment had their antihypertensive drug therapy tapered (as necessary) and discontinued, with a minimum

antihypertensive-free period of 18 days and a preferred washout period of 4 weeks before they began the PEAR study.

Consecutive participants who were enrolled in the PEAR study at the University of Florida (Gainesville, FL) between February 2008 and January 2009 and who were randomly assigned to atenolol as their first study drug were invited to participate in this pilot PEAR substudy. The protocol was approved by the University of Florida Institutional Review Board, and all study patients provided written informed consent to participate in the main PEAR study as well as this pilot substudy (registered at ClinicalTrials.gov as NCT00607347). For those who consented to participate, their dosage of atenolol had to be titrated to 100 mg/day to be included in this PEAR substudy. Atenolol 100 mg/day was selected as this is the typical maximum dose used in clinical practice. Patients receiving atenolol 50 mg/day were not studied because this dose is less likely to cause adverse metabolic effects, and the 3-week duration of treatment at this lower dose would likely have been insufficient for observation of the full metabolic effects of the drug.

Study Protocol

Participants came to the University of Florida General Clinical Research Center (GCRC) after a total of at least 8 weeks of receiving atenolol therapy, with 5 of those weeks at a dosage of 100 mg/day. They were asked to avoid any fruit juices for 4 days before the study visit. Each participant was asked to follow their usual daily diet; no other dietary or drug treatment restrictions were given during the study. Patients fasted overnight for at least 10–12 hours before reporting to the GCRC at 8:00 A.M. on the study day. After collection of data on height, weight, blood pressure, and heart rate, a forearm vein was cannulated with a plastic catheter. Fasting blood samples were collected for measurement of glucose, insulin, triglyceride, high-density lipoprotein cholesterol (HDL), and total cholesterol levels. At 8:30 A.M., atenolol (Atenolol; Sandoz Inc., Princeton, NJ,) 100 mg was orally administered, and blood was collected in heparinized Vacutainers (Becton-Dickinson, Franklin Lakes, NJ) for analysis of plasma atenolol concentration at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after atenolol administration. Blood samples for measuring HDL, triglyceride, and total cholesterol levels were collected in Vacutainers with ethylenediaminetetraacetic acid (Becton-Dickinson).

All patients underwent a 2-hour oral glucose tolerance test (OGTT) 1 hour after atenolol administration, whereby they were given a 75-g glucose solution (S/P lemon lime glucose tolerance beverage; Cardinal Health, McGaw Park, IL) to drink. Glucose and insulin levels were measured during the OGTT every 30 minutes by collecting blood samples in Vacutainers with sodium fluoride for the measurement of glucose and in serum separator tubes for insulin. After separation of the plasma, the samples were frozen and stored at -20°C until assayed. Patients were fed a standard meal after the end of the OGTT. Patients went home after the 12-hour blood sample and returned for the final 24-hour sample. Compliance with the drug treatment was assessed in all patients by tablet count and plasma drug analyses.

Laboratory Measurements

Plasma atenolol concentrations during the pharmacokinetic study visit at the end of 8 weeks of atenolol therapy were determined by liquid chromatography with tandem mass spectrometry based on a previously published method.¹⁶ Briefly, the mobile phase consisted of 94% acetonitrile, 0.5% acetic acid, and 0.04% trifluoroacetic acid and deionized water. The flow rate was 0.5 ml/minute and the analytic column was a Betasil Silica-100, 50 × 3 mm, 5 micron (Thermo-Electron Corp., Bellfonte, PA). Plasma samples were processed by protein precipitation with acetonitrile, and atenolol-d7 was used as the internal standard. The

assay was linear across the concentration range of 5.00–1000 ng/ml. The within-run and between-run precision values (coefficients of variation) for the quality control samples were less than 8.0%, and the accuracy expressed as the relative error was 11.8% or less.

Samples resulting from the OGTT were measured locally, as they were unique to this PEAR substudy, whereas samples collected in the fasting state were measured as part of the main PEAR study at the PEAR central laboratory (Mayo Clinic, Rochester, MN). Specifically, glucose concentrations during an OGTT were measured on a YSI model 2300 STAT PLUS analyzer (YSI Inc., Yellow Springs, OH) by using glucose oxidase enzyme at the GCRC laboratory, University of Florida. Insulin concentrations during the OGTT were measured on a Roche/Hitachi Modular (Roche Diagnostics, Indianapolis IN) by Shands Laboratories, Gainesville, Florida. Fasting plasma glucose, triglyceride, and HDL concentrations were measured on a Hitachi 911 Chemistry Analyzer (Roche Diagnostics) at the PEAR central laboratory (Mayo Clinic). Glucose, triglyceride, and HDL concentrations were determined spectrophotometrically by automated enzymatic assays. Plasma insulin concentrations were measured by using the Access Ultrasensitive Insulin immunoassay system (Beckman Instruments, Chaska, MN). All samples were tested in duplicate, and data reported are the mean of the duplicate samples.

Pharmacokinetic Data Analysis

Plasma atenolol concentration data were analyzed by using noncompartmental pharmacokinetic methods with use of WinNonlin software, version 2.1 (Pharsight Corp., Mountain View, CA). Terminal elimination half-life was assessed by linear regression of the terminal log concentration-time data. Area under the concentration-time curve (AUC) within one dosing interval (AUC_{0-24}) at steady state was calculated by using the trapezoidal rule. Maximum concentration and time of maximum concentration were observed directly from the measured data.

Pharmacodynamic Data Analysis

Homeostatic model assessment (HOMA) of insulin resistance was calculated as the product of basal glucose (mmol/L) and insulin (μ IU/ml) concentrations divided by 22.5, and HOMA of β -cell function was computed as 20 times the basal insulin (μ IU/ml) concentration divided by value of basal glucose concentration (mmol/L) minus 3.5.¹⁷ The AUC values for glucose and insulin during the OGTT (AUC_{0-2}) were calculated by the trapezoidal rule.

Statistical Analysis

This was a pilot study designed to assess the relationship between atenolol concentrations and glucose and insulin concentrations and, if relationships were evident, controlled for potentially relevant clinical variables. As this was a pilot study, where type II errors are at least as serious as type I errors, no adjustment for multiple comparisons was made. Any significant findings will need confirmation in a future study. Fifteen patients provided 80% power at a p value of 0.05, two-sided, to detect a target population correlation of 0.62 between log atenolol AUC and log glucose AUC from the OGTT. We used natural logarithms to limit the effect of outliers. We normalized atenolol AUC_{0-24} by body weight before log transformation, denoted as AUC_n . Descriptive statistics are given as mean $\pm$ SD. To assess the association of atenolol AUC_n with change in the dependent variables, for any variables with a p value less than 0.15, we conducted a forward stepwise regression, forcing the weight-normalized log atenolol AUC_n into the model and stopping when no variable, adjusted for those previously entered, achieved a p value less than 0.05, two-sided. Independent variables considered for model inclusion were baseline levels of fasting glucose, insulin, triglycerides, HDL, and total cholesterol, as well as sex, age, body weight, smoking status, body mass index (BMI), systolic and diastolic blood pressure, hip

circumference, and waist circumference. Secondly, we correlated the weight-normalized log atenolol AUC_n with changes (from baseline to week 8 of atenolol treatment) in triglyceride, glucose, HDL, total cholesterol, and insulin levels. The changes in clinical laboratory values from baseline to the end of treatment were compared by paired *t* test. All statistical analyses were two-sided, conducted by using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 20 patients were enrolled and 15 patients completed the study (six men, nine women). Four patients declined to participate after consenting, and consent was obtained from one patient taking 50 mg/day but the dose was never titrated to 100 mg/day. Patients received atenolol therapy for an average of 8 weeks. Patient characteristics for those completing the pharmacokinetic study are reported in Table 1. The mean $\pm$ SD age was 46 ± 9 years, and most patients were female (60%), Caucasian (80%), and overweight with a BMI of 28.5 ± 5.9 kg/m² and waist circumference of 35.9 ± 6.4 inches. These characteristics were not significantly different from the overall PEAR population enrolled at the University of Florida (all $p > 0.05$).

The atenolol AUC₀₋₂₄ was normalized with respect to body weight (AUC_n) because atenolol AUC₀₋₂₄ was associated with body weight ($r = -0.65$, $p = 0.009$) and BMI ($r = -0.57$, $p = 0.025$), as might be anticipated given the doses were not weight normalized. Mean, SD, and coefficient of variation of atenolol AUC₀₋₂₄, glucose AUC₀₋₂, and insulin AUC₀₋₂ values and other atenolol pharmacokinetic estimates are reported in Table 2. Atenolol pharmacokinetic parameters and the variability in the pharmacokinetic parameters (Figure 1) are consistent with those reported in previous literature.^{12, 18} During the 2-hour OGTT, the mean glucose AUC₀₋₂ was 241.4 mg•hour/dl and mean insulin AUC₀₋₂ was 119.8 μ IU•hour/ml. During atenolol treatment, fasting glucose levels increased from 81.7 ± 9.9 to 85.5 ± 9.1 mg/dl ($p = 0.08$), with minimal changes in levels of fasting insulin (from 8.0 ± 4.9 to 8.4 ± 6.5 μ IU/ml), triglycerides (from 141.1 ± 90.1 to 153.0 ± 104.1 mg/dl), HDL (from 48.4 ± 16.3 to 49.7 ± 19.8 mg/dl), and total cholesterol (from 206.0 ± 39.5 to 203.1 ± 40.8 mg/dl). None of these represented statistically significant changes in metabolic parameters after 8 weeks of atenolol treatment (all $p > 0.05$).

When considering the drug-induced changes in fasting metabolic parameters, we did not find any significant associations between atenolol AUC_n and changes in levels of triglycerides ($r = 0.13$, $p = 0.63$), HDL ($r = -0.08$, $p = 0.76$), total cholesterol ($r = -0.11$, $p = 0.71$), and insulin ($r = -0.23$, $p = 0.39$), although change in glucose level ($r = 0.43$, $p = 0.11$) met our criteria for further adjusted regression analysis.

When evaluating the glucose and insulin data from the OGTT, no significant relationship was noted between atenolol AUC_n and log glucose AUC ($r = 0.08$, $p = 0.78$). However, a significant inverse correlation was noted between atenolol AUC_n and log insulin AUC ($r = -0.69$, $p = 0.004$).

As planned, we performed a forward stepwise regression of atenolol AUC_n versus the variables in the univariate analysis that were observed to have an association *p* value less than 0.15 (log insulin AUC during OGTT and atenolol-induced change in fasting glucose level). In this analysis, the significant univariate association between atenolol AUC_n and log insulin AUC was no longer evident when controlling for other variables such as body weight and BMI ($p = 0.38$; Table 3). In contrast, the association between the atenolol AUC_n and atenolol-induced change in fasting glucose level, which was of borderline significance in univariate analysis, became significant when controlling for sex ($p = 0.0025$; Table 3). No

other clinical variables were significant in the stepwise regression model. Atenolol AUC_n correlated with the change in fasting plasma glucose level in women ($r=0.83$, $p=0.005$), but was not significant in men ($r=0.48$, $p=0.33$).

To better understand these findings, we analyzed the patients based on high waist circumference (men ≥ 40 in. and women ≥ 35 in., according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III guidelines for metabolic syndrome¹⁹) to evaluate if this was influencing the sex-dependent difference seen in the atenolol AUC association with glucose level change; however, this did not provide additional insights into the sex-specific association. The atenolol concentrations may, however, provide some insights into the sex-dependent finding. Specifically, atenolol AUC in women ranged from 6211.62–16,434.02 ng•hour/ml, with a mean of 11,071.76 ng•hour/ml; in men, AUC ranged from 5163.73–12,740.60 ng•hour/ml, with a mean of 8622.98 ng•hour/ml.

Discussion

β -Adrenergic receptor blockers decrease insulin sensitivity, an effect observed with nonselective β -blockers as well as selective β -blockers that are given in doses at which they lose their specificity, and bind to β_2 -adrenergic receptors located in the pancreas.^{20–22}

We hypothesized that the occurrence of metabolic abnormalities (e.g., increased fasting plasma glucose levels, increased plasma triglyceride levels) with atenolol are concentration related and that subjects with higher plasma atenolol exposure are more likely to develop these adverse metabolic effects. We did not find any association between atenolol AUC_n and log glucose AUC_{0–2} during OGTT, but we observed a significant sex-dependent association between atenolol AUC_n and change in fasting plasma glucose level.

β -Blockers increase blood glucose concentrations, which contributes to their propensity to cause new cases of diabetes.^{4, 21, 23, 24} We observed a significant correlation between atenolol AUC_n with change in glucose level after atenolol treatment in women. However, given our small sample size of 15 patients, with only nine women and six men, our ability to fully understand the sex effect noted here is limited. Women had a wider range of AUC and glucose response, and thus it is possible that there is not a true sex effect, but that the greater spread of data in women made observation of an atenolol concentration–glucose level change relationship easier. Further studies should be conducted to confirm whether there is an association between atenolol exposure and adverse effects on glucose level, and whether this is confined to women.

The negative correlation between atenolol AUC_n and log insulin AUC_{0–2} was no longer significant after adjustment for body weight and BMI, suggesting the univariate association was dependent on body size. The exact mechanism by which β -blockers elevate blood glucose levels is uncertain, but since β_2 -adrenergic receptor blockade reduces insulin secretion in response to glucose, this is the most commonly attributed mechanism.²⁵

In this pilot study, patients were taking atenolol 50 mg/day for 3–4 weeks, after which they took atenolol 100 mg/day for at least 4–5 weeks, with the study conducted after 8–9 weeks of atenolol treatment. Even in this short period of time and with a limited sample size, we were able to observe a positive association between atenolol exposure and increased fasting plasma glucose level. To the best of our knowledge, no previous studies have assessed the influence of atenolol exposure on drug-associated increases in glucose and triglyceride levels.

Our pilot study with a small sample size limits our statistical power, and our observation that women had a higher chance of having a change in glucose level associated with atenolol exposure needs to be confirmed. We studied patients only during treatment with the 100-mg/day dose of atenolol since the 50-mg/day dose was less likely to cause adverse metabolic effects, the duration of treatment at 50 mg/day (3 wks) was probably insufficient to observe the full metabolic effects, and there was an expected sufficient variability in atenolol AUC with the 100-mg dose.

Conclusion

We observed that atenolol exposure was significantly associated with atenolol-induced increases in fasting plasma glucose levels during short-term treatment with atenolol when controlled for the sex variable. All patients in this study were taking atenolol 100 mg/day. These data suggest that patients with increased atenolol exposure may be at increased risk for adverse effects on fasting glucose levels. Additional studies are needed to confirm this concentration–adverse response relationship and to more fully explore whether differences really exist in the association based on sex, and if confirmed, to better characterize the mechanisms for this relationship.

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Figure 1.

Scatterplot shows the variability in the weight-normalized log atenolol area under the concentration-time curve within one dosing interval (AUC_n) and the atenolol maximum concentration (C_{max}).

Table 1

Baseline Demographic and Clinical Characteristics of the 15 Study Patients

Characteristic	Value
No. (%) of Patients	
Sex	
Male	6 (40)
Female	9 (60)
Race	
Caucasian	12 (80)
African-American	3 (20)
Mean $\pm$ SD	
Age (yrs)	46 $\pm$ 8.9
Blood pressure (mm Hg)	
Systolic	133.1 $\pm$ 13.2
Diastolic	81.9 $\pm$ 6.8
Body mass index (kg/m ²)	28.5 $\pm$ 5.9
Waist circumference (in.)	35.9 $\pm$ 6.4
Hip circumference (in.)	38.2 $\pm$ 12.1
Fasting plasma levels	
Glucose (mg/dl)	81.8 $\pm$ 7.8
Insulin (μ IU/ml)	8.3 $\pm$ 7.5
Triglycerides (mg/dl)	149.9 $\pm$ 85.0
HDL (mg/dl)	50.5 $\pm$ 19.2
Total cholesterol (mg/dl)	191.7 $\pm$ 33.9
Homeostatic model assessment	
Insulin resistance	1.7 $\pm$ 1.6
β -Cell function	182.8 $\pm$ 143.0
Estimated GFR (ml/min/1.73 m ²) ^a	115.2 $\pm$ 29.8

HDL = high-density lipoprotein cholesterol; GFR = glomerular filtration rate.

^aEstimated GFR calculated by using the four-variable Modification of Diet in Renal Disease study (MDRD) equation: $186 \times \text{serum creatinine concentration}^{-1.154} \times \text{age}^{-0.203} \times (1.210 \text{ for African-Americans}) \times (0.742 \text{ for females})$.

Pharmacokinetic Estimates for Atenolol and AUC Values for Glucose and Insulin During Oral Glucose Tolerance Testing

Table 2

Variable	Atenolol Parameters						Glucose AUC ₀₋₂ (mg•hr/dl)	Insulin AUC ₀₋₂ (μIU•hr/ml)
	AUC ₀₋₂₄ (ng•hr/ml)	C _{max} (ng/ml)	Half-life (hrs)	T _{max} (hrs)	Vd/F (L)	Cl/F (ml/min)		
Mean	10,092.3	1187.5	6.5	2.6	100.0	182.3	241.4	119.8
SD	3253.7	280.9	1.5	0.9	32.7	60.8	54.3	104.7
CV	32.3	23.6	23.0	33.7	32.7	33.3	22.5	87.3
Minimum	5163.7	577.5	4.7	1.5	63.6	101.7	190.7	36.6
Maximum	16,434.0	1751.6	10.7	4.0	191.5	323.3	369.7	410.1

AUC₀₋₂₄ = area under the concentration-time curve within one dosing interval; C_{max} = maximum concentration; T_{max} = time to maximum concentration; Vd/F = volume of distribution, where F = bioavailability; Cl/F = clearance; AUC₀₋₂ = area under the concentration-time curve during 2-hour oral glucose tolerance test; SD = standard deviation; CV = coefficient of variation.

Table 3

Univariate and Stepwise Adjusted Analysis for Log Insulin AUC During Oral Glucose Tolerance Testing and Atenolol-Induced Change in Glucose

Dependent Variable	Covariate Entered	Estimate	Standard Error	p Value
OGTT log insulin AUC				
Unadjusted	Atenolol AUC _n	-1.03	0.32	0.008 ^a
Adjusted for BMI ^b	Atenolol AUC _n	-0.32	0.35	0.38
Fasting glucose change				
Unadjusted	Atenolol AUC _n	7.97	3.8	0.06 ^a
Adjusted for sex ^b	Atenolol AUC _n	12.14	3.1	0.0025

OGTT = oral glucose tolerance test; AUC = area under the concentration-time curve; AUC_n = weight-normalized area under the concentration-time curve within one dosing interval.

^a Only 14 of the 15 patients who had complete data in all fields were included in the analysis.

^b No other covariates entered the model as significant after adjustment for BMI.