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SPECIAL ARTICLE

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Effects of orange juice on the pharmacokinetics of atenolol

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Abstract *Objective*: Fruit juices can significantly change the pharmacokinetics of several drugs. Our objective was to investigate the effect of orange juice on the pharmacokinetics of the beta-blocking agent atenolol.
Methods: In a randomized cross-over study with two phases and a washout of 2 weeks, ten healthy volunteers took either 200 ml orange juice or water thrice daily for 3 days and twice on the fourth day. On the morning of day 3, each subject ingested 50 mg atenolol with an additional amount of either 200 ml orange juice or water. The plasma concentrations of atenolol and the cumulative excretion of atenolol into urine were measured up to 33 h after its dosing. Systolic and diastolic blood pressures and heart rate were recorded in a sitting position before the intake of atenolol and 2, 4, 6, and 10 h after.
Results: Orange juice decreased the mean peak plasma concentration (C_{max}) of atenolol by 49% (range 16–59%, $P < 0.01$), and the mean area under the plasma atenolol concentration–time curve ($AUC_{0\text{-}33\ h}$) by 40% (range 25–55%, $P < 0.01$). The time of the peak concentration (t_{max}) and the elimination half-life ($t_{1/2}$) of atenolol remained unchanged by orange juice. The amount of atenolol excreted into urine was decreased by 38% (range 17–60%, $P < 0.01$), but the renal clearance remained unaltered. The average heart rate was slightly higher during the orange juice + atenolol phase than during the water + atenolol phase.
Conclusions: Orange juice moderately interferes with the gastrointestinal absorption of atenolol. This food–drug interaction can be of clinical significance.

Keywords Orange juice · Atenolol · Bioavailability · Food–drug interaction

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Introduction

Fruit juices can significantly affect the pharmacokinetics of several drugs. Grapefruit juice can greatly increase plasma concentrations of many CYP3A4 substrate drugs (e.g., felodipine, lovastatin, simvastatin, buspirone, cisapride, triazolam, and sildenafil) mainly by inhibiting their first-pass metabolism [1, 2, 3, 4, 5, 6, 7, 8]. Recently, it has been reported that grapefruit juice, and also orange juice, can markedly lower plasma concentrations of certain drugs, e.g., the antihistamine fexofenadine and the beta-adrenoceptor blocking agent celiprolol [9, 10, 11]. The exact mechanism(s) (of the interactions) by which grapefruit juice and orange juice decrease plasma drug concentrations is not known.

Atenolol is a cardioselective beta-blocker that is widely used e.g., in the treatment of angina pectoris, hypertension, and cardiac arrhythmias. It has a mean oral bioavailability of about 50% due to incomplete absorption [12]. Atenolol is a hydrophilic compound that is metabolized only in negligible amounts, and less than 5% of the drug is bound to plasma proteins. Of the bioavailable fraction of atenolol, about 90% is eliminated via the kidneys in unchanged form. It has a mean elimination half-life of about 6 h [13]. As a poorly metabolised compound, atenolol could be considered not to be susceptible to pharmacokinetic drug interactions. However, because orange juice has greatly reduced plasma concentrations of celiprolol, which is also a beta-blocker with a negligible metabolism [14], we found it important to investigate the possible effect of orange juice on the pharmacokinetics and pharmacodynamics of atenolol.

Methods

Study design

Ten healthy volunteers (all men, age range 20–26 years, weight range 63–85 kg) participated in the study. Each

subject was ascertained to be in good health by means of a medical history, clinical examination, and routine laboratory tests, including a standard 12-lead electrocardiogram. Only subjects with a normal PQ interval and a resting pulse rate of 50–80 beats per minute were recruited. The subjects were not regularly using any medication, and all were nonsmokers. The consumption of orange and grapefruit products during the study (from 1 week before the first study day) was forbidden. The study protocol was approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care of the Helsinki and Uusimaa Hospital District and by the Finnish National Agency for Medicines. The subjects gave their written informed consent before entering the study.

A randomized cross-over study design with two phases was used at an interval of 2 weeks. The volunteers ingested 200 ml orange juice or water three times a day (at 0600–0800, 1100–1300, and 1900–2100 hours) for 3 days and, on day 4, at 0600–0800 hours and noon until 1300 hours. The orange juice used was a product diluted by the manufacturer from a concentrated whole fruit juice (Valio Appelsiini Täysmehu; Valio Ltd., Helsinki, Finland). On day 3, each subject was given 50 mg atenolol (Atenblock 50 mg tablet, Generics, Potters Bar, England) with an additional amount of 200 ml orange juice or water at 0900 hours. The volunteers fasted overnight before the administration of atenolol. Subjects were served a warm meal 3 h after the intake of atenolol, and 7 h after atenolol intake they were given a light meal. They were not allowed to drink coffee, tea, or cola during the study days.

Blood sampling and determination of drug concentrations

On the third study day, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples were drawn into siliconized plastic tubes containing ethylene diamine tetraacetic acid (Terumo Europe, Leuwen, Belgium) before administration of atenolol and 1, 2, 3, 4, 6, 8, 10, 12, 24, and 33 h after. Plasma was separated within 30 min and stored at −70°C until analyzed.

The urine was collected cumulatively from 0 h to 33 h in the fractions 0–12, 12–24, and 24–33 h. The volume was measured, and 5 ml of each fraction was stored at −70°C until analyzed.

Plasma and urine atenolol concentrations were quantified by means of a high-performance liquid chromatography method [15] that involved solid phase extraction and ultraviolet detection. The limit of detection was 10 ng ml^{-1}. The between-day coefficient of variation (CV) for determination of plasma atenolol was 14.2% at 13.8 ng ml^{-1} ($n=9$), 2.3% at 120 ng ml^{-1} ($n=10$), and 1.0% at 779 ng ml^{-1} ($n=10$). The between-day CV for determination of urine atenolol was 9.3% at 0.7 μg ml^{-1} ($n=2$), 0.7% at 5.91 μg ml^{-1} ($n=2$), and 3.8% at 16.6 μg ml^{-1} ($n=2$).

Blood pressure and heart rate

Before administration of atenolol and at 2, 4, 6, and 10 h after, the systolic and diastolic blood pressures and heart rate were measured twice from the forearm with the subject in a sitting position, and the mean value was used in the calculations. The blood pressures and heart rate were measured using an automatic oscillometric blood pressure monitor (HEM-711; Omron Healthcare Gmbh, Hamburg, Germany). Average values for heart rate and blood pressures were calculated by dividing the area under the effect–time curve from 0 h to 10 h by 10 h.

Pharmacokinetic calculations

The peak concentration of atenolol in plasma (C_{max}) and time to C_{max} (t_{max}) were obtained directly from the original data. The terminal log-linear phase of the plasma atenolol concentration–time curve was identified visually for each subject. The elimination rate constant (k_{el}) was determined using linear regression analysis of the log-linear part of the plasma concentration–time curve. The area under the atenolol concentration–time curve from time 0 to 33 h ($AUC_{0\text{-}33\ h}$) was calculated using the linear trapezoidal rule, and the $AUC_{0\text{-}\infty}$ with extrapolation to infinity by dividing the last measured concentration by k_{el}. The elimination half-life ($t_{1/2}$) was determined using the following equation: $t_{1/2} = \ln 2/k_{el}$. The renal clearance (Cl_{ren}) of atenolol was calculated from the amount of atenolol excreted into urine from 0 h to 33 h divided by the $AUC_{0\text{-}33\ h}$.

Statistical analysis

The data are expressed in the text and table as mean ± SD, except for t_{max}, which is expressed as median and range. For clarity, in Fig. 1, the data are expressed as mean ± SEM. The pharmacokinetic and pharmacodynamic data were analyzed using the Student t-test (two-tailed) for paired values or, in the case of t_{max}, the Wilcoxon test. In addition, for all pharmacokinetic parameters, 90% confidence intervals (CIs) were calculated for the ratio orange juice phase to water phase. The statistical program Systat for Windows, Version 6.0.1 (Systat, Evanston, IL, USA) and the MK model Version 5 (Biosoft, Cambridge, UK) were used for the analysis. Differences were considered to be statistically significant at $P < 0.05$.

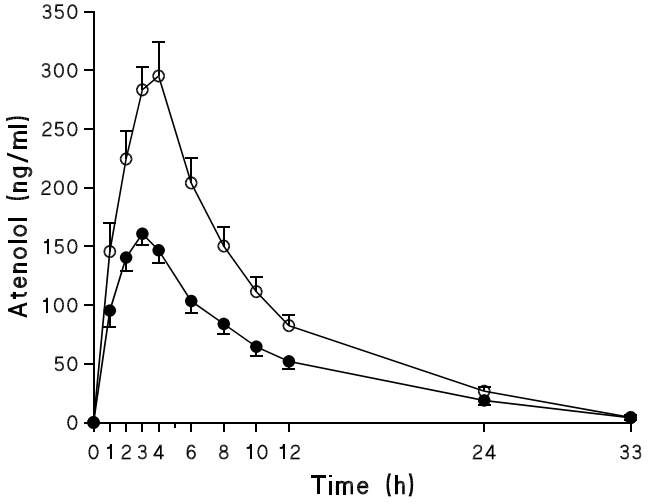

Fig. 1 Plasma concentrations (mean values ±SEM) of atenolol in ten healthy subjects after a single oral dose of 50 mg atenolol; after ingestion of 200 ml orange juice (*solid circles*) or water (*open circles*) three times a day for 3 days; and on day 3 1 h before, with atenolol and 4 h and 10 h after atenolol administration. In addition, 200 ml orange juice or water was ingested at 0800 hours and 1300 hours on day 4

Results

Pharmacokinetics

Plasma concentrations of atenolol were moderately decreased by orange juice (Fig. 1 and Table 1).

In each of the ten subjects the C_{max}, $AUC_{0\text{-}33\ h}$, and Ae of atenolol were smaller during the orange juice phase than during the water phase. Orange juice reduced the mean C_{max} and $AUC_{0\text{-}33\ h}$ of atenolol by 49% (range 16–59%, $P < 0.01$) and 40% (range 25–55%, $P < 0.01$), respectively. Orange juice did not change the t_{max} or elimination $t_{1/2}$ of atenolol. The Ae of atenolol was decreased by 38% (range 17–60%, $P < 0.01$), but the Cl_{ren} remained unaltered by orange juice.

Pharmacodynamics

During the orange juice phase, the average heart rate was significantly higher than during the water phase ($P < 0.01$; Table 1). The maximal change in heart rate after atenolol intake was not different between the phases. There were no significant differences in the systolic and diastolic blood pressures between the two phases. Atenolol was well tolerated during both study phases.

Discussion

The aim of the present study was to investigate whether orange juice affects the pharmacokinetics of atenolol. Orange juice reduced the C_{max}, AUC, and urinary excretion of atenolol by 49, 40, and 38%, respectively, but did not alter its elimination half-life or renal clearance. Orange juice reduced the bioavailability of atenolol in each subject and the effect was fairly uniform; the decrease in the AUC of atenolol ranged from 25% to 55% and in its urinary excretion from 17% to 60%.

In contrast to grapefruit juice, orange juice has had no effect on the pharmacokinetics of CYP3A4 substrates felodipine and cyclosporine [1, 16]. However, in recent studies, both grapefruit and orange juice have reduced considerably the AUC of fexofenadine and celiprolol [9, 10, 11]. It has been suggested that the mechanism by which orange juice (and other fruit juices) markedly reduces the bioavailability of fexofenadine involves inhibition of function of OATP located in the intestinal

Table 1 The pharmacokinetic and hemodynamic variables of atenolol in ten healthy volunteers after ingestion of a single dose (50 mg) of atenolol after pretreatment with water (control) or orange juice. Pharmacokinetic and pharmacodynamic data are mean values ±SD, t_{max} values are given as median with ranges, C_{max} peak plasma concentration, t_{max} time to reach C_{max}, $t_{1/2}$ half-life, $AUC_{0\text{-}33\ h}$ area under the plasma concentration-time curve from 0 h to 33 h, $AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from 0 h to infinity, *Ae* amount excreted, Cl_{ren} renal clearance

Variable	Water (control)	Orange juice	90% CI for ratio
C_{max} (ng ml^{-1})	319.0 ± 81.4	163.6 ± 29.6*	0.39–0.63
Percentage of control (range)	100	51 (41–84)	
t_{max} (h)	3.5 (3–4)	3.0 (2–4)	0.69–0.91
$t_{1/2}$ (h)	6.4 ± 1.2	7.7 ± 2.4	0.95–1.45
$AUC_{0\text{-}33\ h}$ (ng ml h^{-1})	2,853 ± 881	1,700 ± 565*	0.50–0.69
Percentage of control (range)	100	60 (45–75)	
$AUC_{0\text{-}\infty}$ (ng ml h^{-1})	2,960 ± 890	1,833 ± 616*	0.52–0.71
Percentage of control (range)	100	62 (43–78)	
Ae (mg)	24.6 ± 4.4	15.3 ± 2.7*	0.52–0.73
Percentage of control (range)	100	62 (40–83)	
Cl_{ren} (ml min^{-1})	149.0 ± 25.3	158.9 ± 40.6	0.99–1.14
Average heart rate (beats per minute)	51.8 ± 5.0	56.7 ± 6.6*	
Average systolic blood pressure (mmHg)	113.8 ± 12.6	114.5 ± 13.2	
Average diastolic blood pressure (mmHg)	66.0 ± 7.4	66.5 ± 7.8	

* $P < 0.01$ versus control phase

wall. Also, the orange juice–celiprolol interaction may involve inhibition of intestinal uptake transporter(s).

In our previous study, orange juice lowered the AUC of celiprolol much more (83%) than that of atenolol in the present study (by 40%). Both celiprolol and atenolol are hydrophilic, weak bases that are eliminated into urine mainly as parent drugs. However, atenolol is even more hydrophilic than celiprolol, and its molecular weight (266) is smaller than that of celiprolol (416), which would enable also a paracellular absorption [17, 18]. While celiprolol is a substrate for the efflux transporter P-glycoprotein, and possibly for other transporters, there seems to be no data on transporters involved in the absorption of atenolol [14]. Furthermore, the dose-dependent pharmacokinetics of celiprolol and the linear pharmacokinetics of atenolol could be explained by different roles of transporters in their absorption. Thus, atenolol is probably less susceptible to a marked pharmacokinetic interaction with orange juice due to inhibition of transporter(s) in the intestinal wall. However, orange juice could interfere also with paracellular permeation of atenolol during its absorption. An unspecific food effect leading to release of bile acids and their complexation with atenolol in the intestine might have contributed to reduced absorption of atenolol when coingested with orange juice [19, 20, 21, 22]. In addition, also drug formulation could be a confounding factor in relation to the impact of orange juice on atenolol bioavailability.

To conclude, orange juice moderately reduces the bioavailability of atenolol. Coadministration of orange juice with atenolol may necessitate its dose adjustment, or they should be given separately.

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Conflict of interest: No information supplied

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