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# Effects of Cranberry Juice on Pharmacokinetics of β-Lactam Antibiotics following Oral Administration▽

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**Cranberry juice consumption is often recommended along with low-dose oral antibiotics for prophylaxis for recurrent urinary tract infection (UTI). Because multiple membrane transporters are involved in the intestinal absorption and renal excretion of β-lactam antibiotics, we evaluated the potential risk of pharmacokinetic interactions between cranberry juice and the β-lactams amoxicillin (amoxicilline) and cefaclor. The amoxicillin-cranberry juice interaction was investigated in 18 healthy women who received on four separate occasions a single oral test dose of amoxicillin at 500 mg and 2 g with or without cranberry juice cocktail (8 oz) according to a crossover design. A parallel cefaclor-cranberry juice interaction study was also conducted in which 500 mg cefaclor was administered with or without cranberry juice cocktail (12 oz). Data were analyzed by noncompartmental methods and nonlinear mixed-effects compartmental modeling. We conclude that the concurrent use of cranberry juice has no significant effect on the extent of oral absorption or the renal clearance of amoxicillin and cefaclor. However, delays in the absorption of amoxicillin and cefaclor were observed. These results suggest that the use of cranberry juice at usual quantities as prophylaxis for UTI is not likely to alter the pharmacokinetics of these two oral antibiotics.**

Urinary tract infections (UTIs) are diagnosed at least once in approximately 50 to 60% of all women in the United States during their lifetimes (11, 24). The prevalence of UTIs is significantly less in young men and increases in older age (10). A considerable portion of the patients experience multiple recurrences (1). Long-term low-dose antibiotic therapy is often recommended as prophylaxis for recurring UTI for 6 months to a year or longer (28). In addition to standard treatments of trimethoprim-sulfamethoxazole and nitrofurantoin, β-lactam antibiotics are also prescribed for pediatric and adult patients with recurrent UTIs caused by organisms that are resistant to standard therapy and that have appropriate susceptibilities (24, 36, 37).

Cranberry juice has been the most widely used natural remedy for UTIs in the past decades (13, 25). Multiple clinical trials have demonstrated the benefit of the daily intake of cranberry juice cocktail (CJC; containing 27% pure juice) as prophylaxis for UTIs (3, 14, 16, 31, 38). Although cranberry juice is often used in combination with low-dose oral antibiotics, little is known about its drug interaction potential. It is now known that fruit juices are capable of producing clinically significant drug interactions through the inhibition of carrier-mediated active transport (6). For example, the levels of absorption of fexofenadine (7), talinolol (29), and celiprolol (21) were markedly reduced by the concurrent ingestion of grapefruit, orange, and apple juices. Although the molecular mechanisms of intestinal transport remain largely unknown, the furanocoumarins and bioflavonoids present in these juices were shown to be potent in vitro inhibitors of organic anion-transporting polypeptides and are suggested to play a role in the observed juice interactions (7). Grapefruit juice coadministration also led to twofold increase in the renal clearance ($CL_R$) of nicotine (13, 15). These results suggest that fruit juice constituents and/or their by-products, when they are present at sufficient concentrations, may be capable of modulating transporter-mediated intestinal absorption and the systemic disposition of β-lactam antibiotics.

Despite their low lipophilicities and zwitterionic nature at physiological pH, both amoxicillin (amoxicilline) and cefaclor exhibit good oral bioavailabilities (22, 39). There is ample evidence in the literature to suggest that carrier-mediated active transport plays an important role in the intestinal absorption of many β-lactam antibiotics (30). We previously demonstrated the involvement of multiple drug transporters in the disposition of β-lactams (17, 19). Human oligopeptide transporter 1 (hPepT1), expressed on the intestinal mucosa brush border membrane, transports both amoxicillin and cefaclor and may mediate their active intestinal absorption (19). Renal apical transporter human oligopeptide transporter 2 (hPepT2) also mediates the efficient uptake transport of both antibiotics. In addition, we observed significant amoxicillin uptake by recombinant human organic anion transporter 3 (hOAT3) in cell-based assays. hOAT3 is primarily expressed in the basolateral domain of the renal tubular epithelium. Our in vitro results suggest that these β-lactams may undergo active secretion as well as active reabsorption in the kidney (19).

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Similar to citrus juices, cranberry juice has a rich content of flavonoids and phenolic acids. Quercetin and benzoic acid are the major flavonoid and phenolic acids, respectively, in CJC (4). Using a cell expression system, we observed that CJC inhibited recombinant hPepT1-mediated cellular uptake of amoxicillin and cefaclor in a concentration-dependent manner (data not shown). Hippuric acid, the major urinary metabolite of benzoic acid, was also shown to be a potent hOAT3 inhibitor ($K_i$, 20 μM) and may be capable of inhibiting hOAT3-mediated amoxicillin secretion in vivo (5, 17, 35).

The emerging literature and our preliminary in vitro data led to the present hypothesis that the constituents of cranberry juice and/or their in vivo metabolites may interact with intestinal and renal drug transporters and alter the pharmacokinetics of amoxicillin and cefaclor. Accordingly, we investigated the potential juice-antibiotic interaction in a group of healthy women. The results of our study should clarify the risk, if any, in the event that an oral β-lactam antibiotic is used with cranberry juice.

## MATERIALS AND METHODS

**Material.** CJC containing 27% cranberry juice was supplied by Fisher BioServices Corporation in collaboration with Ocean Spray Cranberries, Inc. It was formulated under contract with the National Center for Complementary and Alternative Medicine for use in several clinical trials on the efficacy of cranberry juice for the prophylaxis and treatment of UTIs. Its composition was characterized to meet research needs and is similar to that of the retail product.

**Study population.** The studies were conducted at the University of Washington General Clinical Research Center. The study protocol and consent form were approved by the Institutional Review Board at the University of Washington. Because UTIs are much more prevalent in women than men, we enrolled only female subjects in the studies. Two separate groups of 18 healthy women were each enrolled in studies with amoxicillin and cefaclor. The subjects had no known allergies to β-lactam antibiotics, had no history of renal or liver disease, and were not receiving concurrent medications except oral contraceptives ($n$ = 3 in the amoxicillin study and $n$ = 2 in the cefaclor study). All individuals provided written informed consent before participation. A sample size of 18 was estimated to be sufficient for the detection of at least a 25% difference in the area under the concentration-time curve (AUC) and $CL_R$ with 80% power at an α level of 0.05 for both amoxicillin and cefaclor.

**Study design.** The subjects were instructed to abstain from eating citrus fruits and fruit juices for 7 days before the study and during the course of the study. Food containing caffeine and alcoholic beverages were not permitted 24 h before the study and during study visits since caffeine and its metabolites are known to interfere with some transporter functions (18, 26).

The subjects were assigned to each of the four following treatments according to a fixed-sequence crossover design: (i) 500 mg amoxicillin with 8 oz water, (ii) 500 mg amoxicillin with 8 oz CJC, (iii) 2 g amoxicillin with 8 oz water, and (iv) 2 g amoxicillin with 8 oz CJC. Each treatment was separated by a washout period of at least 1 week.

Prior to each visit with juice treatment, the subjects took an additional 8 oz CJC twice daily for 2 days to approximate chronic juice dosing. Two amoxicillin doses (500 mg and 2 g) were included in the study to differentiate the mechanism of inhibition of intestinal absorption (competitive versus noncompetitive), if one was present. Blood (10 ml) was drawn from an indwelling venous catheter predosing and at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 h following the administration of a single oral dose of amoxicillin with 8 oz water or CJC. Serum was separated by centrifugation at 3,000 rpm and was stored at −78°C until analysis. Urine samples were collected just before and at 2-h intervals for 8 h after antibiotic dosing.

The cefaclor-CJC interaction was investigated in a crossover randomized study similar to that described above for amoxicillin-CJC. The subjects took a single oral dose of 500 mg cefaclor with 12 oz water or CJC after an overnight fast. The treatments were separated by 1 week. For the juice treatment, the subjects took an additional 12 oz CJC twice daily for 2 days prior to the study day. A standard lunch was provided 4 h postdosing to minimize any interference from the effects of food. Blood (10 ml) was drawn from an indwelling venous catheter and placed into prechilled heparin-coated tubes prior to and at 0.25, 0.5, 1, 1.5, 2, 3, 4, and 6 h after antibiotic dosing. Plasma samples were immediately separated at 4°C and were stored at −78°C in cryovials containing 25% glacial acetic acid (100 μl per ml plasma). Urine samples were collected just before and at 2-h intervals for 6 h postdosing and were stored at −78°C until analysis.

**Sample analysis.** Amoxicillin concentrations in serum and urine were analyzed by previously reported high-pressure liquid chromatography methods with either liquid chromatography-mass spectrometry (LC-MS) or UV detection (2). The cefaclor concentrations in plasma were analyzed by a modification of the LC-MS method with amoxicillin. A 50-μl plasma sample was mixed with 80 μl ion-pairing reagent (1% triethylamine and 1% acetic acid), 10 μl 5% acetic acid, and 20 μl internal standard (cefadroxil at 40 μg/ml); and the mixture was then left to stand at room temperature for 5 min. One milliliter acetonitrile was added to precipitate the plasma proteins. The supernatant was transferred and evaporated to dryness under a vacuum. The residue was subsequently reconstituted with 100 μl of formic acid at a concentration of 0.1% (vol/vol). Five microliters of reconstituted plasma supernatant was injected onto a Ultra Aqueous $C_{18}$ column (200 mm by 2.1 mm; particle size, 5 μm; Restek Corp.) connected to an Agilent 1100 LC-MS system. The mobile phase consisted of formic acid (0.1%, vol/vol) at 80% and methanol at 20% and was run for 1 min at a flow rate of 0.25 ml/min, followed by a gradient to 50% methanol at 3 min along with a gradual increase in the flow rate to 0.3 ml/min. The gradient was maintained for another minute and was then increased to 80% methanol to wash out the retained material from the column. The mass selective detector was operated in the atmospheric pressure ionization electrospray mode with positive polarity. The mass ions monitored were $m/z$ 368 for cefaclor and $m/z$ 364 for cefadroxil. The calibration curve was linear over the concentration range tested (0.05 to 10 μg/ml), and the limit of detection of the assay was 0.02 μg/ml. The intra- and interday variations were found to be below 6% and 15%, respectively.

Urine cefaclor concentrations were quantified by a high-pressure liquid chromatography–UV method. Forty-microliter urine samples were acidified with 25 mM phosphoric acid and were mixed with the internal standard (cefadroxil at 1 mg/ml). Ten microliters of sample was injected onto an Ultra Aqueous $C_{18}$ column (150 mm by 4.6 mm; particle size, 5 μm; Restek Corp.), and cefaclor was detected at 265 nm. Chromatographic separation was achieved by gradient elution of the mobile phase, which consisted of $KH_2PO4$ solution (20 mM, pH 3.3) and methanol. The standard curve was linear over the range tested (12.5 to 600 μg/ml), and the detection limit of the assay was 8 μg/ml. The intra- and interday assay precisions were below 5% and 9%, respectively.

**Noncompartmental pharmacokinetic analysis.** Descriptive pharmacokinetic parameters for amoxicillin and cefaclor were estimated by noncompartmental analysis (WinNonlin software, version 3.2; Pharsight Corp, Mountain View, CA). The peak concentration in serum ($C_{max}$) and the time to $C_{max}$ ($T_{max}$) were estimated by visual inspection of the data. The terminal elimination rate constant (β) was determined by linear regression of at least three points in the terminal phase. The AUC was calculated by the log-linear trapezoidal method, and extrapolation to infinity was obtained by dividing the last observed concentration by β. The elimination half-life ($t_{1/2}$) was calculated as 0.693/β. The apparent oral clearance (CL/$F$) was estimated as dose/AUC. Total urinary excretion of the antibiotics over the entire duration of urine collection ($A_e$) was estimated from the urinary antibiotic concentration and the urine volume of each 2-h collection. $CL_R$ was calculated as $A_e$/AUC over the respective sampling duration. The results are expressed as means ± standard deviations (SDs). $T_{max}$ values are presented as medians (ranges). Comparative statistics were calculated by analysis of variance for repeated measures by using SPSS software (version 10.0; SPSS Inc., Chicago, IL) or paired Student's $t$ test. The Wilcoxon rank test was used to compare $T_{max}$ values. A $P$ value of 0.05 or less was considered statistically significant. To perform a bioequivalence test, point estimates and 90% confidence intervals (CIs) for coadministered treatment/control geometric mean ratios were computed for log-transformed parameters ($C_{max}$ and AUC).

**Population pharmacokinetic analysis.** We performed population pharmacokinetic analysis using SPK software (System for Population Kinetics, University of Washington, Seattle, WA) and the NONMEM software system (version V; GloboMax LLC, Ellicott City, MD). Population modeling allows the simultaneous determination of structural model parameters (e.g., CL/$F$ and volume of distribution [$V$]) as well as variability measures, such as the between-subject variability of selected structural model parameters, the variability of parameters among different study occasions, and the residual unexplained variation (RUV; due to model misspecification and measurement error). After consideration of competing models, we chose a one-compartment model with Weibull nonlinear absorption [$w(t)$] and first-order elimination as the structural model. Weibull absorption describes the time-varying absorption rate [$w(t)$; in μg/h] as

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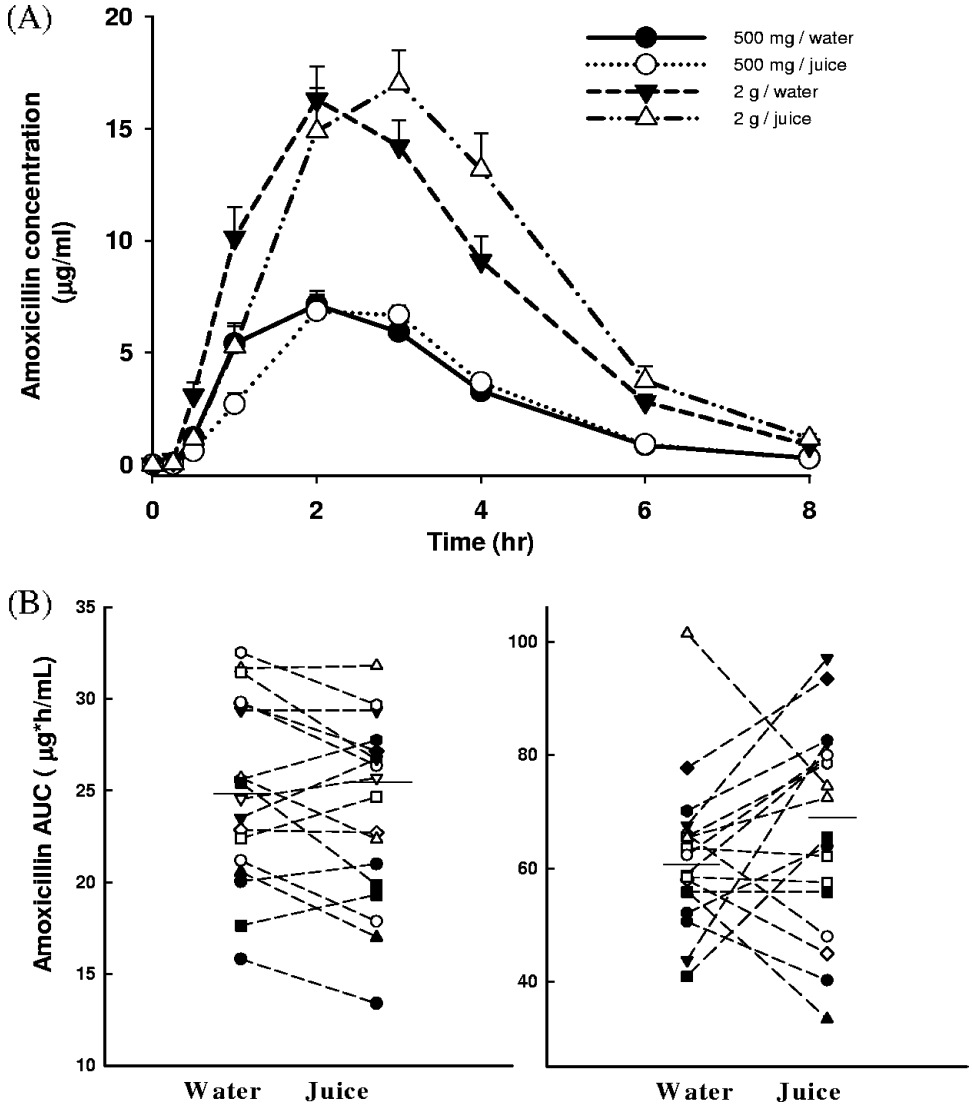


FIG. 1. Effects of cranberry juice on amoxicillin pharmacokinetics. (A) Mean serum amoxicillin concentration-time curve in healthy women following oral administration of amoxicillin at 500 mg or 2 g with 8 oz water or cranberry juice cocktail. Data represent the means ± standard errors of the means ($n = 18$). (B) Individual values of AUC from time zero to infinity with medians in the absence and presence of cranberry juice. The same symbol was used for each subject.

$$w(t) = D\left(\frac{S}{TD}\right)\left(\frac{t}{TD}\right)^{s-1}\exp\left[-\left(\frac{t}{TD}\right)^{s}\right]$$

where $D$ is the dose; $S$ is the shape parameter (unitless) that defines the overall form of the distribution (from a single exponential to a combination of exponential increase and decay); $TD$ (in hours) is the scale parameter and serves to stretch the distribution function along the abscissa, thus affecting both the peak and the time to peak of absorption; and $t$ is time. Serum concentration data were fitted by a one-compartment model with Weibull absorption and first order elimination as

$$\frac{dC(t)}{dt} = w(t) - \frac{\mathrm{CL}/F}{V/F}C(t)$$

where $C(t)$ is the concentration at time $t$. The study design, in which each subject was exposed to all four treatments, allowed us to model both between-subject variability (BSV) and between-occasion variability (BOV) in the pharmacokinetics of amoxicillin and cefaclor. Due to difficulties in obtaining successful estimation convergence by the first-order conditional estimation method, we used the first-order method in our final analyses. The first-order method for population analysis with nonlinear mixed-effects modeling is characterized by an approximation of the population fitting criterion, which usually holds well when the population variability is small. True-likelihood profiling (performed with SPK software) of selected runs indicated that the first-order method performed reasonably well for this analysis.

## RESULTS

**Amoxicillin-juice interaction. (i) Amoxicillin noncompartmental pharmacokinetic analysis.** Eighteen women participated in the amoxicillin-juice interaction study. The mean ± SD age was 28 ± 5 years, and the mean ± SD body weight was 55 ± 12 kg. The mean serum amoxicillin concentration-time profiles after administration of the 500-mg oral dose and the 2-g oral dose are shown in Fig. 1A. The amoxicillin CL/$F$ increased from 347 ± 75.2 ml/min after the administration of the 500-mg dose to 560 ± 112 ml/min after the administration of the 2-g dose ($P < 0.05$). In contrast, the mean amoxicillin

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TABLE 1. Mean serum amoxicillin noncompartmental pharmacokinetics following administration of a 500-mg or a 2-g dose with 8 oz CJC or water in healthy women[a]

| Amoxicillin dose and liquid coadministered | Serum | | | | | Urine | | |
|---|---|---|---|---|---|---|---|---|
| | AUC (μg · h/ml) | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $t_{1/2}$ (h) | CL/*F* (ml/min) | $A_e$ (mg) | Urinary recovery (%) | $CL_R$ (ml/min) |
| 500 mg | | | | | | | | |
| Water | 24.9 (4.81) | 8.76 (1.88) | 2.0 (1–3.0) | 1.13 (0.15) | 347 (75.2) | 308 (52) | 61.6 (10) | 218 (63) |
| CJC | 23.7 (4.91) | 8.27 (2.35) | 2.75 (1–3.5)[b] | 1.05 (0.15) | 367 (91.8) | 320 (74) | 61.4 (11) | 236 (69) |
| 2 g | | | | | | | | |
| Water | 62.0 (13.4) | 19.0 (6.16) | 2.0 (1–4.0) | 1.17 (0.26) | 560 (112) | 806 (146) | 40.2 (7.2) | 227 (47) |
| CJC | 67.3 (18.1) | 21.1 (5.38) | 3.0 (2–4.0)[b] | 1.13 (0.20) | 538 (176) | 864 (249) | 43.2 (12.5) | 226 (58) |

[a] The data for all parameters except $T_{max}$ represent mean values (SDs) for 18 healthy women. $T_{max}$ is represented as median (range). $AUC_{0-\infty}$, AUC from time zero to infinity; CL/*F*, $A_e$, and $CL_R$ are for from 0 to 8 h postdosing.
[b] $P < 0.01$ for comparison of difference between cranberry juice and water treatment at each dose.

$CL_R$ values were similar between the two doses (218 and 227 ml/min for the 500-mg and 2-g doses, respectively) (Table 1). These results suggest that the observed nonlinearity in the disposition of amoxicillin is likely the result of dose-dependent absorption and may involve saturation in hPepT1-mediated amoxicillin transport.

We observed comparable amoxicillin average $C_{max}$ and AUC values following the ingestion of 8 oz water and cranberry juice (Table 1). A bioequivalence test was performed by constructing a 90% CI for the geometric mean AUC and $C_{max}$ ratio between cranberry and water (control) treatment. The 90% CIs of the treatment ratios for both AUC (0.894 to 1.000 for the AUC for the 500-mg dose and 0.919 to 1.241 for the AUC for the 2-g dose) and $C_{max}$ (0.846 to 1.009 for the $C_{max}$ for the 500-mg dose and 0.953 to 1.358 for the $C_{max}$ for the 2-g dose) fell within the FDA-stipulated bounds for bioequivalence of 80% to 125% of the values for the controls for AUC at both doses and $C_{max}$ at the lower dose but not $C_{max}$ at the higher dose. No consistent pattern among the 18 subjects in the intraindividual change in the AUC between the two treatments at both doses was detected (Fig. 1B). The observation indicated a minimal effect of cranberry juice on the oral absorption of amoxicillin. Nonetheless, the coadministration of amoxicillin and cranberry juice did result in a significant delay in the amoxicillin $T_{max}$ ($P < 0.01$), suggesting a slower absorption rate in the presence of juice. Neither the amoxicillin elimination $t_{1/2}$ nor the 8-h cumulative urinary excretion differed between the control and the juice treatments, and there was no significant difference in the amoxicillin $CL_R$ (Table 1).

**(ii) Amoxicillin population pharmacokinetic analysis.** In the initial base structural model, we investigated the log-normal BSV of each of the four structural parameters, CL/*F*, *V*/*F*, *S*, and *TD*. Log-normal variability is a flexible statistical distribution widely used in population analysis. It implies that the parameters in the population are strictly positive and characterized by an asymmetric distribution which allows for a long distribution tail at the high-end portion of the parameter distribution. The resulting block diagonal variance-covariance matrix structure included a significant covariance only between *S* and *TD* (implying that these values are correlated in the population). We also found that body weight could significantly ($P < 0.05$) explain some of the BSV seen in the base model. We also explored the BOV of the four structural parameters to investigate whether the pharmacokinetic parameters in the same subject changed significantly between study occasions. The addition of BOV was significant ($P < 0.05$) for each of the four parameters; thus, it was included in the base model (Table 2). The RUV, i.e., the variation in the observations which is not accounted for by the population model, was best represented by an additive error model. Subsequently, addition of dose and juice as covariates indicated that both significantly ($P < 0.05$) explained some of the BOV seen in the base model. We also found that body weight could significantly ($P < 0.05$) explain some of the BSV seen in the base model. Thus, the covariate structure for the *TD* parameter was modeled by using indicator variables of 0 or 1 to indicate concomitant juice or no juice and, likewise, to indicate the low or the high amoxicillin dose. The covariate structure for CL/*F* was formulated in terms of the low or the high antibiotic dose, and

TABLE 2. Estimates of amoxicillin population pharmacokinetic parameters in base and final models

| Model and parameter | Parameter estimate ± SE | BSV (%) | BOV (%) |
|---|---|---|---|
| Base model | | | |
| CL/*F* (ml/min) | 453 ± 31.3 | 15.3 | 29.3 |
| *V*/*F* (liters) | 28.9 ± 1.82 | 77.6 | 52.0 |
| *S* (unitless) | 2.73 ± 0.145 | 32.1 | 42.9 |
| *TD* base (h) | 1.65 ± 0.084 | 10.6 | 20.1 |
| Residual error (additive, μg/ml) | 0.712 | | |
| Final model | | | |
| Baseline CL/*F* (ml/min) | 368 ± 17.4 | 18.1 | 15.0 |
| Increase in CL/*F* at high dose (ml/min) | 177 ± 17.5 | | |
| Baseline *V*/*F* (liters) | 22.5 ± 1.06 | 72.6 | 35.6 |
| Increase in *V*/*F* at high dose (liters) | 12.3 ± 2.83 | | |
| Difference in *V*/*F* due to difference from mean body weight (liter/kg difference from mean) | 0.105 ± 0.093 | | |
| Baseline *S* (unitless) | 2.86 ± 0.11 | 32.9 | 32.7 |
| Baseline *TD* base (h) | 1.31 ± 0.19 | 10.8 | 13.4 |
| *TD*, population value of juice administration (h) | 0.533 ± 0.074 | | |
| *TD*, population value of high dose administration (h) | 0.375 ± 0.164 | | |
| Residual error (additive, μg/ml) | 0.689 | | |

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TABLE 3. Population model-predicted amoxicillin serum pharmacokinetic parameters

| Dose, liquid coadministered | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $AUC_{0-\infty}$[a] (μg · h/ml) |
|---|---|---|---|
| 500 mg, water | 11.1 | 1.7 | 22.6 |
| 500 mg, CJC | 9.3 | 2.2 | 22.6 |
| % Change | −16.2 | 29.4 | 0 |
| 2 g, water | 25.8 | 2.1 | 60.9 |
| % Change, nonlinear dose effect | −41.8 | 23.5 | −32.7 |
| 2 g, CJC | 21.9 | 2.7 | 60.9 |
| % Change from water to CJC | −15.1 | 28.6 | 0 |

[a] $AUC_{0-\infty}$, AUC from time zero to infinity.

the *V*/*F* covariate structure was formulated in terms of the low or the high dose and a linear function of body weight in the final model. While BSV remained approximately the same between the base model and the final model, BOV for all four structural model parameters was significantly ($P < 0.05$) reduced by the inclusion of the juice and the dose covariates. A slight reduction in RUV also was achieved. The final model parameter estimates are shown in Table 2.

Population pharmacokinetic results were found to agree well with those derived from the noncompartmental analysis (Table 3). Compared to the results for the water control, 41%, 28%, and 69% increases in *TD* were predicted following juice coadministration, the use of a higher amoxicillin dose, or juice coadministration and the use of a higher amoxicillin dose combined, respectively. The increase in *TD* correlated well with the increase in $T_{max}$ observed with the coadministration of juice. As an altered *TD* affects both the magnitude of $C_{max}$ and $T_{max}$ in the absorption profile, the increases in *TD* following juice coadministration resulted in a 15.1 to 16.2% reduction in $C_{max}$ and a 28.6 to 29.4% increase in $T_{max}$ compared to the values for the water control at each dose (Table 3). Simulated amoxicillin concentration-time courses based on the population pharmacokinetic model are depicted in Fig. 2.

The model also provides a prediction for dose-dependent relative bioavailability (*F*), which can be validated by using $A_e$ data. In particular, if a constant $CL_R$ is assumed and given the total amount excreted, $A_{e\infty}$, we have

$$\frac{F_{high}}{F_{low}} = \left(\frac{AUC_{high}}{AUC_{low}}\right)\left(\frac{dose_{low}}{dose_{high}}\right) = \left(\frac{A_{e\infty,high}}{A_{e\infty,low}}\right)\left(\frac{dose_{low}}{dose_{high}}\right)$$

where high represents the high dose and low represents the low dose. The values in Table 1 suggest that $CL_R$ is not significantly changed between the low and the high dose; thus, the ratio of the CL/*F* for the low dose and the CL/*F* for the dose estimates approximates relative *F*:

$$\frac{(CL/F)_{low}}{(CL/F)_{high}} = \frac{F_{high}}{F_{low}}$$

Our population pharmacokinetic estimates of CL/*F* support this hypothesis and were consistent with the independent estimate (66%) obtained from the $A_e$ data.

**Cefaclor-juice interaction. (i) Cefaclor noncompartmental pharmacokinetic analysis.** The subjects ($n = 18$) enrolled in the cefaclor study had a mean ± SD age of 31.7 ± 7.4 years and a mean ± SD body weight of 58.7 ± 12.1 kg. Figure 3A shows the mean cefaclor concentration-time curves following the concurrent administration of cefaclor and 12 oz CJC or water. The observed pharmacokinetic parameters (Table 4) were in agreement with the values in the literature (19, 26). Similar to the findings with amoxicillin, we observed a significant decrease in cefaclor $C_{max}$s ($P < 0.01$) and a slightly longer $T_{max}$ ($P > 0.05$) with the concomitant use of cranberry juice, suggesting a slower absorption rate in the presence of the juice. However, there was no difference in the mean AUC between cefaclor coadministration with water and CJC (20.4 and 21.0 μg · h/ml, respectively). Bioequivalence between CJC and the water control was examined by the same method used for amoxicillin analysis. The 90% CIs of the log-transformed treatment ratios for both AUC (0.922 to 1.013) and $C_{max}$ (0.807 to 0.940) were within the bioequivalence bounds of 80% to 125% of the values for the control. The intrasubject changes in the cefaclor AUC between juice and water coadministration are shown in Fig. 3B. While a slightly reduced AUC in the presence of CJC was observed in the majority of subjects, three subjects also exhibited 10 to 20% increases in AUCs. We did not observe a significant difference in cefaclor urinary recovery (75%) and $CL_R$ (306.6 ± 60.2 ml/min) between the water control and juice treatments.

**(ii) Cefaclor population pharmacokinetics.** Cefaclor population pharmacokinetic analysis was performed by using the same approach described above for the analysis of amoxicillin. The addition of BOV was initially significant ($P < 0.05$) for the parameters CL/*F*, *S*, and *TD*; thus, only BOV was included in the base model for these three parameters (Table 5). The RUV was best represented by a proportional error model. The

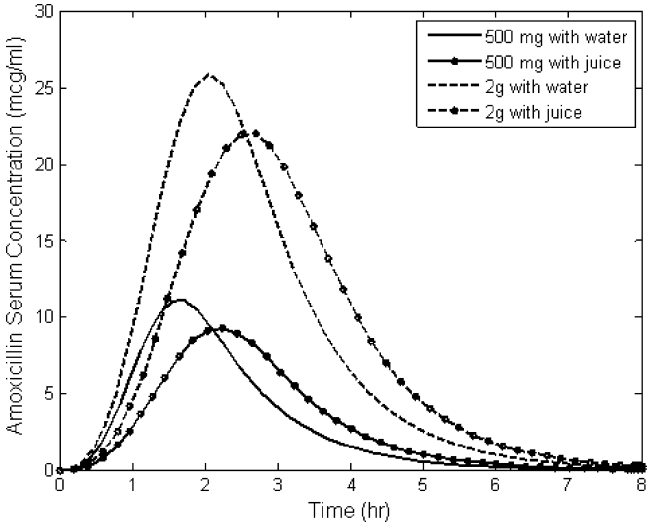


FIG. 2. Simulated concentration-time courses obtained by using the typical value of the parameters in the amoxicillin population pharmacokinetic model for each treatment. Changes in parameter values due to juice coadministration resulted in reduced $C_{max}$s and increased $T_{max}$s. Changes in parameter values due to the higher dose resulted in increased $C_{max}$s and slightly increased $T_{max}$s.

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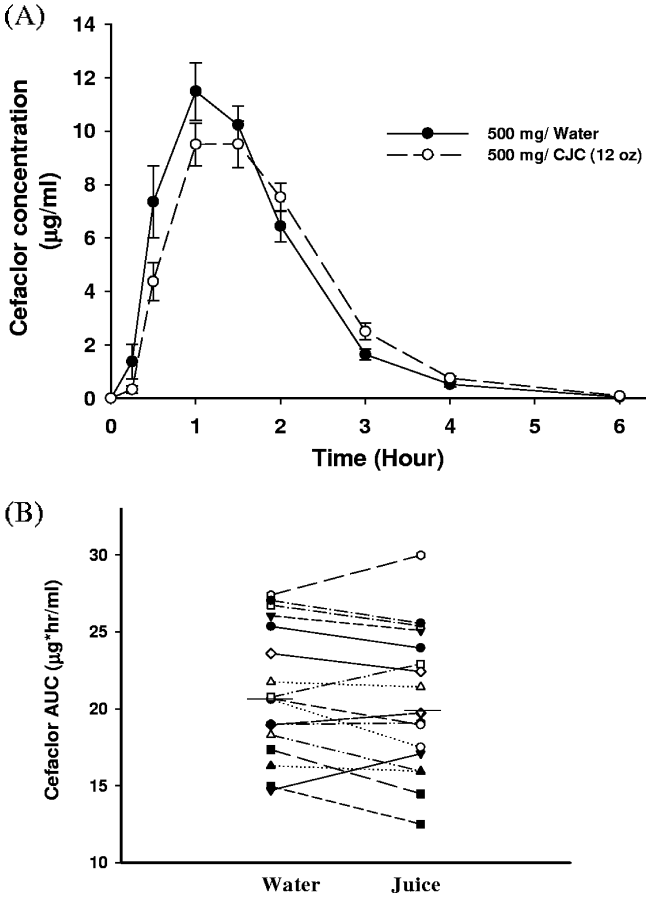


FIG. 3. Effects of cranberry juice on cefaclor pharmacokinetics. (A) Mean cefaclor concentration-time curve in healthy women following oral administration of cefaclor at 500 mg with 8 oz water or CJC. Data represent the means ± standard errors of the means ($n$ = 18). (B) Individual values of the cefaclor AUC from time zero to infinity with medians in the absence and the presence of cranberry juice.

covariate analysis indicated that juice coadministration could significantly ($P < 0.05$) explain some of the BOV seen in the base model and that body weight could significantly ($P < 0.05$) explain some of the BSV seen in the base model. As a result, in the final model we represented the variation in *TD* in terms of juice or no juice administration, while *V*/*F* was modeled as a linear function of body weight. Improvements in the model goodness of fit, as well as some reduction in BSV, were achieved by the addition of covariates in the final model. The residual error (RUV) remained unchanged between the base and the final models.

TABLE 5. Estimates of cefaclor population pharmacokinetic parameters in the base and final model

| Model and parameter | Parameter estimate ± SE | BSV (%) | BOV (%) |
|---|---|---|---|
| Base model | | | |
| CL/*F* (ml/min) | 403 ± 20 | 19.8 | NA[a] |
| *V*/*F* (liters) | 2.16 ± 1.07 | 22.6 | 11.3 |
| *S* (unitless) | 1.640 ± 0.068 | 80.4 | 79.8 |
| *TD* (h) | 0.779 ± 0.050 | 21.3 | 36.9 |
| Residual error (proportional, μg/ml) | 26.2 | | |
| Final model | | | |
| CL/*F* (ml/min) | 407 ± 20.7 | 19.7 | NA |
| *V*/*F* (liters) | 2.15 ± 1.27 | 17.4 | 10.5 |
| Difference in *V*/*F* due to difference from mean body weight (liters/kg) | 0.146 ± 0.043 | | |
| *S* (unitless) | 1.730 ± 0.178 | 69.7 | 55.2 |
| *TD* base (h) | 0.704 ± 0.050 | 26.8 | 27.8 |
| TD, population value of juice administration (h) | 0.160 ± 0.060 | | |
| Residual error (proportional, %) | 26.5 | | |

[a] NA, not available.

As shown in Table 6, estimates of the final cefaclor population pharmacokinetic model parameters agreed well with those obtained from noncompartmental analysis. Similarly to the analysis of amoxicillin, the population modeling enabled more mechanistic quantification of the pharmacokinetics. *TD* was predicted to increase 22.7% with juice coadministration, which resulted in a 10% increase in the calculated $T_{max}$ and an 8.7% decrease in $C_{max}$. Figure 4 shows simulated cefaclor serum concentration-time curves obtained by using the typical population pharmacokinetic parameter values.

## DISCUSSION

Cranberry products have a long history of medical use because of their beneficial effects on human health and are promoted as complementary or alternative means of prophylaxis for UTIs (3, 13, 14, 16, 25, 31, 38). Limited studies have evaluated the drug interaction potential of cranberry juice. Recent studies have shown that cranberry juice potently inhibits CYP3A and CYP2C9 in vitro (9, 34); however, in vivo studies with probe substrates for CYP2C9 (*S*-warfarin),

TABLE 4. Mean noncompartmental cefaclor pharmacokinetic parameters following oral administration of 500 mg with 12 oz CJC or water in healthy women[a]

| Vehicle | Plasma | | | | | Urine | | |
|---|---|---|---|---|---|---|---|---|
| | $AUC_{0-\infty}$ (μg · h/ml) | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $t_{1/2}$ (h) | CL/*F* (ml/min) | $A_e$ (mg) | Urinary recovery (%) | $CL_R$ (ml/min) |
| Water | 21.2 (4.20) | 13.4 (3.50) | 1.25 (0.5–2) | 0.59 (0.09) | 397 (82.7) | 375 (40.4) | 74.9 (8.08) | 307 (60.2) |
| CJC | 20.5 (4.60) | 11.7 (3.02)[b] | 1.5 (1–2.0) | 0.62 (0.08) | 408 (100) | 367 (39.4) | 73.5 (7.89) | 310 (56.6) |

[a] The data for all parameters except $T_{max}$ represent the mean values (SDs). $T_{max}$ values are represented as medians (ranges). $AUC_{0-\infty}$, AUC from time zero to infinity. CL/*F*, $A_e$, and $CL_R$ are for from 0 to 8 h postdosing.
[b] $P < 0.01$ for comparison of difference between cranberry juice and water administration.

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TABLE 6. Population model-predicted cefaclor plasma pharmacokinetic parameters

| Vehicle | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $AUC_{0-\infty}$[a] (μg · h/ml) |
|---|---|---|---|
| Water | 11.5 | 1.6 | 20.3 |
| CJC | 10.5 | 2.2 | 20.4 |
| % Change | −8.7 | 10 | 0.5 |

[a] $AUC_{0-\infty}$, AUC from time zero to infinity.

CYP1A2 (tizandine), and CYP3A4 (midazolam) have not demonstrated an interaction (20). Despite the lack of an effect of cranberry juice on the pharmacokinetics of warfarin (20), several case reports have indicated that cranberry juice results in an enhanced antithrombotic effect of warfarin (8, 12, 23, 27, 32, 33), suggesting a possible pharmacodynamic effect.

A number of studies have reported incidences of apple-, orange-, and grapefruit-drug interactions (6, 7, 21, 29). The potential effect of cranberry juice on drug transporters had not been investigated prior to our study. Given the involvement of drug transporters in the active intestinal absorption and renal excretion of the β-lactams, in the present study we examined the potential of their interaction with CJC in healthy women. Two antibiotics exhibiting different absorption characteristics were chosen for the studies. On the basis of the dose-dependent absorption, amoxicillin absorption is shown to be mediated by passive diffusion and active transport; while it is more hydrophilic, the intestinal absorption of cefaclor is mainly an active process (30).

Following the concurrent consumption of CJC at 8 to 12 oz, the common doses used for UTI prophylaxis, we did not observe a significant difference in the amoxicillin and the cefaclor AUCs in the female subjects. Hence, regular-strength CJC at the quantity usually consumed has little effect on the extent of amoxicillin and cefaclor oral absorption. In view of our positive in vitro findings of hPepT1 inhibition by CJC, the negligible in vivo effect of juice may be explained by sufficient fluid dilution of the ingested juice in the gastrointestinal tract as well as the limited residence time of the inhibitory components of CJC in the small intestine. Both factors would reduce the extent and duration of CJC inhibition in vivo. In addition, the passive diffusion of amoxicillin across the intestinal epithelium is also likely to lower the magnitude of any transporter-based interaction. Even though CJC did not affect the extent of absorption, our noncompartmental model analysis suggested that these antibiotics have slower absorption rates in the presence of the juice. This was substantiated by our population pharmacokinetic analysis, which allowed us to fully model the changes in $C_{max}$ and $T_{max}$ following juice administration. Cranberry juice intake is predicted to lead to a notable increase in $T_{max}$ and a decrease in $C_{max}$ for both amoxicillin and cefaclor (Fig. 2 and 4). The underlying mechanism(s) of the absorption rate change is not known. It could be the result of a modest inhibition of hPepT1 by juice, which affects only the rate but not the extent of the absorption. We also cannot rule out the possibilities of other nonspecific effects of juice in the gut, such as an altered drug dissolution rate or ionization due to changes in gastric pH.

Renal tubular secretion serves as an efficient means of targeting antibiotics to the urinary tract for the treatment of infection. Factors affecting proximal tubular secretion, such as the suppression of OAT3- and PepT2-mediated transport, may have a direct impact on the efficacies of antibiotics for the treatment of UTIs. As shown by our results, CJC at 8 to 12 oz did not elicit significant interference with the $CL_R$ of amoxicillin and cefaclor. The lack of a systemic effect of juice may reflect the low circulating concentrations of inhibitory juice constituents and its metabolite(s) following the intake of CJC.

Like amoxicillin and cefaclor, other β-lactams, such as cefixime and cefadroxil, exhibit similar disposition pathways, including PepT1-mediated active absorption in the intestine as well as active renal tubular transport in the kidneys. Our results suggest that these other β-lactams may also be safely coadministered with cranberry juice at the usual daily amounts for the prophylaxis of UTI without significant pharmacokinetic interactions. Nonetheless, as the effect of juice could be variable, depending on the specific pharmacokinetic properties of the antibiotics, along with administration-related factors, such as the concentration and volume of the juice ingested, we cannot entirely exclude the potential risk of an antibiotic-cranberry juice interaction in the case of concurrent antibiotic use and the consumption of a large volume of concentrated cranberry juice.

In conclusion, the results of the studies with humans described here indicate that while the concomitant administration of CJC results in a modest delay in amoxicillin absorption and a slight delay in cefaclor absorption, their total absorption and $CL_R$ were not affected and the delays were deemed to be not clinically significant. Therefore, our results do not support a clinically relevant interaction between β-lactam antibiotics and cranberry juice at the amounts regularly consumed.

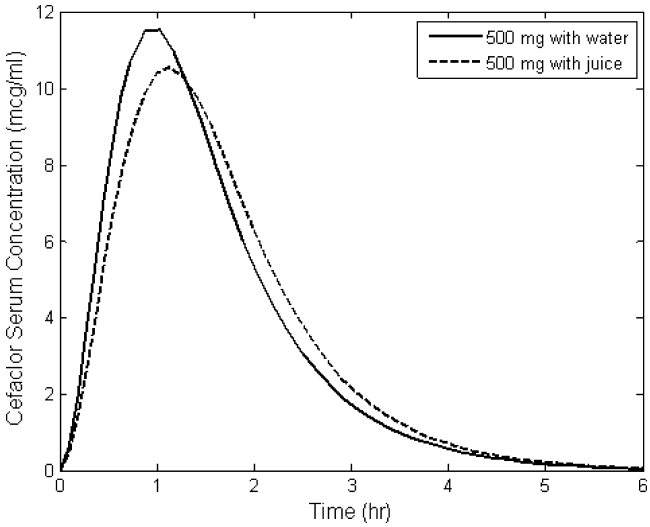


FIG. 4. Simulated concentration-time courses obtained by using the typical value of parameters in the cefaclor population pharmacokinetic model for each treatment. Changes in parameter values due to juice coadministration resulted in reduced $C_{max}$s and increased $T_{max}$s.

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