ARTICLE

The Pharmacokinetic Exposure to Fexofenadine is Volume-Dependently Reduced in Healthy Subjects Following Oral Administration With Apple Juice

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Pharmacokinetic exposures to fexofenadine (FEX) are reduced by apple juice (AJ); however, the relationship between the AJ volume and the degree of AJ-FEX interaction has not been understood. In this crossover study, 10 healthy subjects received single doses of FEX 60 mg with different volumes (150, 300, and 600 mL) of AJ or water (control). To identify an AJ volume lacking clinically meaningful interaction, we tested a hypothesis that the 90% confidence interval (CI) for geometric mean ratio (GMR) of FEX AUCAJ/AUCwater, AUCAJ 300mL/AUCwater, and AUCAJ 600mL/AUCwater are 0.903 (0.752–1.085), 0.593 (0.494–0.712), and 0.385 (0.321–0.462), respectively. While a moderate to large AJ-FEX interaction is caused by larger volumes of AJ (e.g., 300 mL to 600 mL), the effect of a small volume (e.g., 150 mL) appears to be clinically not meaningful.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Exposures to FEX are reported to be remarkably reduced following FEX administration with a large volume of AJ in healthy subjects.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ The study addresses the question on the relationship between the volume of AJ and degree of AJ–FEX interaction and identifies at least one volume of AJ lacking a clinically meaningful interaction.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?
✔ The results demonstrate a volume-dependent reduction in FEX AUC following oral administration of FEX with 150 mL to 600 mL of AJ. While a moderate to large AJ-FEX interaction is caused by larger volumes of AJ (e.g., 300 mL to 600 mL), the effect of a small volume (e.g., 150 mL) appears to be clinically not meaningful.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND TRANSLATIONAL SCIENCE?
✔ The AJ–FEX pharmacokinetic interaction may be a clinical concern only when relatively large volumes of AJ are coingested, but not when a small volume of AJ is taken with FEX.

Fexofenadine (FEX) is an antihistamine compound that is widely used in the treatment of allergy, including seasonal rhinitis and chronic urticaria.1 FEX is known as a substrate for organic anion-transporting polypeptides (OATPs), i.e., OATP1A2, OATP2B1, and P-glycoprotein (P-gp),1–4 and coadministrations with drugs such as itraconazole and rifampicin cause significant drug interactions.1,5,6 Food and beverages are also associated with altered pharmacokinetics of FEX.1–3,7 Our previous study has demonstrated a remarkable reduction in area under the plasma concentration–time curve (AUC) of FEX when taken orally with a large volume (1,200 mL) of apple juice (AJ).3 Thus, the pharmacokinetic interaction with AJ is recognized as a significant therapeutic concern. However, the relationship between the volume of AJ and the degree of reduction in FEX AUC is not clearly understood, although volume dependency is reasonably assumed.

Therefore, with a hypothesis that a smaller volume of AJ (e.g., a glass of AJ) may not meaningfully reduce the AUC of FEX, the present study investigated the effect of three different volumes of AJ on the pharmacokinetics of FEX in healthy subjects.

METHODS

Ten healthy Japanese volunteers (six men and four women; age range, 20–35 years; body mass index range, 18–23 kg/m²) participated in this clinical trial. Each subject was ascertained to be in good health as assessed by medical history, physical examination, 12-lead electrocardiogram, and routine laboratory testing including complete blood counts, serum chemistry, and urinalysis. Subjects were not using...
any medication or dietary supplements and all were non-smokers. Pregnant women were excluded. Participation in any other clinical trial within 2 months, blood donations >400 mL within 2 months or >200 mL within 1 month, and other incongruence with study protocol were key exclusion criteria. Alcoholic drinks and caffeine-containing food and beverages were prohibited 1 day before and during the study. Consumption of grapefruit, orange, and apple products except those provided in this study was forbidden within 2 weeks before drug administration. The study protocol was reviewed and approved by the Institutional Review Board of Oita University Hospital. Written informed consent was obtained from all subjects prior to study participation. This clinical trial has been registered with the Japan Clinical Trials Registry (http://www.umin.ac.jp/ctr/index.htm) number UMIN000014773.

Study design
This study was a single-dose, open-label, 4-way, well-balanced crossover trial. Each subject was randomly allocated to one of the 10 random sequences generated by computer software (Excel 2007, Microsoft, Tokyo, Japan). Following the overnight fast (from 10:00 pm to drug administration), subjects received an oral dose of FEX (Allegra, Sanofi K.K., Tokyo, Japan) 60 mg with AJ and/or water simultaneously at 9:00 am. The volume of AJ and water were:

A: FEX (60 mg) + AJ 0 mL + Water 600 mL
B: FEX (60 mg) + AJ 150 mL + Water 450 mL
C: FEX (60 mg) + AJ 300 mL + Water 300 mL
D: FEX (60 mg) + AJ 600 mL + Water 0 mL

The 10 subjects (Allocation Numbers 001 through 010) received FEX in the order of ACDB, CBAD, DABC, BDCA, ABDC, DABC, BCAD, BCDA, CABD, BCDA, respectively.

The AJ (Martinelli, Watsonville, CA) used in this study was nonconcentrated. Subjects were required to be semirecumbent for 4 h after drug administration until standardized lunch was served. Venous blood (9 mL) was sampled into tubes containing heparin before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11 h after administration of FEX. Following centrifugation at 2,000g at 4°C for 10 min, plasma was separated immediately and frozen at –80°C until analysis. The washout interval between periods was at least 1 week.

Assay of plasma FEX concentrations
The plasma concentrations of FEX were quantified by high-performance liquid chromatography (HPLC, Agilent Technologies 1220 Infinity LC, Tosoh, Tokyo, Japan) with a fluorescence detection method that had been previously developed and modified in our department. Plasma samples were purified by the solid-phase extraction method outlined previously. Briefly, the cartridge columns (BondElut C18, 3 mL, 500 mg, Agilent Technologies, Lake Forest, CA) used for the extraction were washed with methanol (2 mL), water (2 mL), and 0.2 M sodium acetate buffer (pH 4.0, 1.5 mL) in that order. Diphenhydramine (1,000 ng/mL) 100 μL as the internal standard (I.S.) mixed with 0.9 mL of 0.2 M sodium acetate buffer (pH 4.0) was added to the plasma 1 mL. Following passing the plasma mixture, the C18 columns were washed with water 2 mL, methanol/water (50/50, v/v) 2 mL, and methanol 1 mL in turn. Then the C18 columns were dried with an air flow for 20 min. Finally, the sample was eluted with 1 mL of 50 mM triethylamine in methanol and evaporated to dryness at 40°C in a vacuum. The residue was dissolved in a 200 μL aliquot of HPLC mobile phase composed of acetonitrile/ammonium acetate (28/72 (v/v), pH 8.3). The solution (100 μL) was injected into an analytical column (X-Bridge C18 5 μM, 150 × 4.6 mm, Waters, Milford, MA) with a mobile flow rate of 1.0 mL/min. The temperature of the column was 40°C. The fluorescence of excitation wavelength was 232 nm and emission wavelength was 310 nm. The retention times of FEX and I.S. were 8 and 21 min, respectively. The calibration curves of FEX were linear over concentrations ranging from 1 to 500 ng/mL in plasma (r = 0.9994). The limit of quantification was 1 ng/mL. The within-day coefficient of variations (CVs) were 8.3% at 1 ng/mL and 1.6% at 100 ng/mL (n = 5). The between-day CVs were 10.6% at 1 ng/mL and 5.6% at 100 ng/mL (n = 3).

Pharmacokinetic analysis
Analysis of the pharmacokinetic parameters for FEX was performed with noncompartmental analysis by WinNonlin (v. 6.4, Pharsight, Mountain View, CA). The maximum plasma concentration (Cmax) and time to reach Cmax (tmax) were observed from the plasma concentration–time data directly. The area under the plasma drug concentration–time curve from 0 h to infinity (AUC0–∞) was calculated using the log-linear trapezoidal method with extrapolation to infinity. The terminal elimination rate constant (λ) was calculated by log-linear regression of the final data points (at least 3). The elimination half-life (t1/2) was calculated by ln2/λ. The CL/F was determined by the oral dose / AUC0–∞.

Statistical analysis
The primary end point of this study was the geometric mean ratio (GMR) of FEX AUCAJ/AUCwater. We considered that bio-comparability would be established if the 90% confidence interval (CI) of the GMR of FEX AUCAJ/AUCwater was contained within the bound of 0.5–2.0. The FEX AUCwater was assumed to be 1,342 ± 519 ng·h/mL (mean ± standard deviation, SD), the data based on our previous study,3 to determine the sample size in the present study. Ten subjects were required to determine the bio comparability with 80% power even if the true GMR of AUCAJ/AUCwater was 0.8. The AUC and Cmax were assumed to be log-normally distributed, and analyzed by the linear mixed effects models, where the conditions (e.g., AJ vs. water) and the study periods were regarded as fixed effects and the subject as a random effect. For the primary purpose of this study, lack of significant interaction with AJ was to be concluded when at least one volume was associated with the lower bound of 90% CI of GMR for AUCAJ/AUCwater being above 0.5. All statistical analyses were performed by the statistical software R (https://www.r-project.org/).

RESULTS
As described, 10 subjects (male, six; female, four) completed the study protocol and there were no adverse events for any subjects during the study periods.
The mean ± SD plasma concentration–time curves following a single oral dose of FEX 60 mg administered with water 600 mL (the control), AJ 150 mL followed by water 450 mL, AJ 300 mL followed by water 300 mL or AJ 600 mL are shown in Figure 1, the individual changes of AUC with different volumes of AJ are shown in Figure 2, and the pharmacokinetic parameters are summarized in Table 1. The reduction in AUC and C_{max} by AJ were clearly volume-dependent. Reduction in AUC for FEX with AJ 300 mL and 600 mL were statistically significant compared with control (water). GMR of AUC_{AJ 300mL}/AUC_{water} and AUC_{AJ 600mL}/AUC_{water} were 0.583 (90% CI, 0.494–0.712) and 0.385 (90% CI, 0.321–0.462), respectively. The 90% CI for GMR of AUC of FEX with AJ 300 mL and 600 mL did not fall into the bound of 0.5–2.0. Reduction in AUC for FEX with AJ 150 mL was not statistically significant compared with control (water). GMR of AUC_{AJ 150mL}/AUC_{water} was 0.903 (90% CI, 0.752–1.085), with the 90% CI for GMR of AUC of FEX with AJ 150 mL being contained within the bound of 0.5–2.0. Similarly, reduction in C_{max} for FEX with AJ 300 mL and 600 mL were statistically significant compared with control (water). GMR of C_{max AJ 300mL}/C_{max water} and C_{max AJ 600mL}/C_{max water} were 0.538 (90% CI, 0.421–0.687) and 0.370 (90% CI, 0.290–0.473), respectively. The 90% CI for GMR of C_{max} of FEX with AJ 300 mL and 600 mL did not fall into the bound of 0.5–2.0. Reduction in C_{max} for FEX.
with AJ 150 mL was not statistically significant compared with control (water). GMR of C_{max} AJ 150 mL/C_{max} water was 0.849 (90% CI, 0.664–1.086). The 90% CI for GMR of C_{max} of FEX with AJ 150 mL was contained within the bound of 0.5–2.0. The median t_{max} of FEX with water, AJ 150 mL, 300 mL, and 600 mL were 2.0, 2.5, 3.0, and 3.0 h, respectively, with no apparent difference observed between AJ volume conditions.

**DISCUSSION**

In the present study, we observed a volume-dependent effect of AJ on the pharmacokinetics of FEX as demonstrated by reduction in the AUC of various degrees when different volumes of AJ were ingested. As expected based on data from our previous study, 3 administration of FEX ingested with a relatively large volume of AJ, given 600 mL in this study, resulted in a remarkable reduction in the AUC of FEX. While 300 mL AJ led to a moderate reduction compared with control (water), 150 mL of AJ exhibited only a modest reduction in the AUC of FEX. The degree of pharmacokinetic interaction with 150 mL of AJ was considered clinically not meaningful since the 90% CI for GMR of AUCs was contained within the prespecified comparability bound of 0.5–2.0. The rationale for selecting this bound was internally discussed prior to the conduct of this study based on data from clinical trials, including one dose-ranging study, where the safety and efficacy of FEX were tested in patients with idiopathic urticaria. 9 In their study, 20 mg b.i.d. of FEX appeared to relieve the symptoms of chronic idiopathic urticaria compared with placebo, although the change from baseline in the mean daily pruritus score following 20 mg b.i.d. was slightly smaller than that observed with 120 mg b.i.d.; 20 mg, –38%; 120 mg, –43%. 9 Interestingly, in their covariate analysis, FEX 20 mg b.i.d. seemed to be as efficacious as FEX 60 mg b.i.d. for reducing itching in patients with a lower baseline pruritus score while 20 mg b.i.d. did not improve itching as effectively as 60 mg b.i.d. in those patients with a higher baseline pruritus score. 9 The authors inferred from this observation that FEX exposures reduced even by half would still maintain its efficacy in the majority, if not all, of patients with allergic symptoms of mild to moderate intensity. Thus, the lower end of the bound (0.5) was set somewhat arbitrarily but as a clinically acceptable margin. The upper end of the bound was justified since the safety profile of higher doses (e.g., 120 mg b.i.d. or 240 mg b.i.d.) of FEX than recommended (i.e., 60 mg b.i.d.) seemed to be clinically acceptable. 1,9 Based on the wide therapeutic index of FEX established with linear pharmacokinetics, 10 the selected bound of 0.5–2.0 was deemed to be reasonable for testing the comparability of the pharmacokinetics of FEX.

The exact mechanism by which AJ interacts with FEX to alter its pharmacokinetics is not fully understood. In our previous study, the uptake of FEX was higher with OATP2B1 cRNA-injected *Xenopus laevis* oocytes than that with the water-injected oocytes 2 and the uptake of FEX was decreased by AJ in vitro. 11 Interestingly, another in vitro study showed that OATP1A2 was the key transporter responsible for the uptake of FEX in the intestine among OATPs, 2,12 although Glaeser et al. reported OATP1A2 and OATP2B1 were detected in intestinal biopsies. 12 It is important to note that FEX is also a substrate for P-gp, OATP1B1, and OATP1B3, 1,4,7,13–15 P-gp has been assessed as an important efflux transporter for FEX, 1,4,7,13 and it is believed that efflux of FEX is potentially inhibited by quercetin, one of the active components of AJ. 16 To increase the AUC and C_{max} of FEX, 17 OATP1B1 and OATP1B3 are mainly expressed on the sinusoidal membrane of human hepatocytes, 1,13 and were suggested to contribute to the hepatic uptake of FEX. 1,7,13–15 The effect of AJ on hepatic uptake transporters should be negligible, because if hepatic uptake of FEX were inhibited by AJ, the exposure to FEX would be increased. Although the FEX exposures were decreased with AJ in the present study, there were no significant differences in FEX elimination half-lives between the groups. The effect of AJ on the intrinsic clearance of FEX should also be negligible. Overall, an altered bioavailability is presumably responsible for the observed interaction between FEX and AJ in this study through intestinal OATP2B1 and/or OATP1A2.

Several specific ingredients in fruit juices have been shown to play a role in drug–fruit juice interactions. For example, phloridzin and phloretin were demonstrated as stronger inhibitors for OATP2B1 among substances in AJ and the mixture of flavonoids including phloridzin, phloretin, hesperidin, and quercetin caused more potent inhibition of uptake of estrone-3-sulfate, a substrate of OATP2B1, into *Xenopus* oocytes expressing OATP2B1. 18 Although naringin, 18 quercetin, apigenen, and kaempferol 19 were revealed to

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**Table 1** Pharmacokinetic parameters of FEX (60 mg) following oral administration with different volumes of AJ in healthy subjects

| Parameters          | Water (N=10) | 150 mL AJ (N=10) | 300 mL AJ (N=10) | 600 mL AJ (N=10) |
|---------------------|--------------|------------------|------------------|------------------|
| AUC_{0-\infty} (ng h/mL) | 1,736 ± 462  | 1,598 ± 496      | 1,072 ± 429      | 668 ± 163        |
| GMR                 | 0.903        | 0.593            | 0.385            |                  |
| 90% CI              | 0.752–1.085  | 0.494–0.712      | 0.321–0.462      |                  |
| AUC_{0-\infty} (ng h/mL) | 1,529 ± 452  | 1,401 ± 458      | 932 ± 375        | 569 ± 151        |
| C_{max} (ng/mL)     | 303 ± 132    | 257 ± 119        | 158 ± 56         | 108 ± 51         |
| GMR                 | 0.849        | 0.538            | 0.370            |                  |
| 90% CI              | 0.664–1.086  | 0.421–0.687      | 0.290–0.473      |                  |
| t_{max} (h)         | 2.0 (1.5–6.0)| 2.5 (1.5–6.0)    | 3.0 (2.0–6.0)    | 3.0 (3.0–6.0)    |
| CL/F (L/h/kg)       | 0.6 ± 0.2    | 0.7 ± 0.1        | 1.1 ± 0.4        | 1.7 ± 0.3        |

Data are given as mean ± standard deviation, except for t_{max} with median and range. AUC_{0-\infty}, area under the plasma concentration–time curve extrapolated to infinite time; GMR, geometric mean ratio; CI, confidence interval; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; CL/F, apparent oral clearance; AJ, apple juice; FEX, fexofenadine.
Impact of Apple Juice Volume on Fexofenadine PK
Luo et al.

Affect the uptake of FEX mediated by OATP2B1 in vitro, the concentrations of these substances in AJ were much lower than their IC values for OATP2B1 inhibition. Catechins extracted from green tea have been observed to inhibit the uptake function of OATP1A2 and OATP2B1 in vitro and in a clinical study green tea reduced plasma concentrations of nadolol in healthy subjects, potentially due to inhibition of OATP1A2 by catechins. Therefore, catechins may be a possible factor to interact with FEX, although this has not been evaluated in humans.

The other possible factors to be discussed for an AJ–FEX interaction include changes in pH in the gastrointestinal tract, which may be temporarily altered by ingestion of AJ, resulting from the acidity of AJ. The pH may potentially affect the absorption of drugs through altering dissolution of drugs. However, it is known that FEX is a zwitterionic compound and dissolvable with a broad pH range, hence the pH effect should be negligible in dissolving this drug. Gastrointestinal pH may directly affect the activity of intestinal transporters. OATPs have exhibited pH-dependent transport of various organic anions in vitro and especially OATP2B1 has been observed to transport estrone-3-sulfate more effectively at acidic pH than neutral. Therefore, in theory, the acidity of AJ could accelerate OATP2B1-mediated drug transport in vitro; however, that is very unlikely the case in vivo since AJ did not increase but in fact decreased FEX exposures in the present study. Changes in gastrointestinal pH by AJ, if any, should play a minor role in governing OATP2B1 activities.

We observed a tendency of delay in tmax with higher volumes of AJ, although it was not statistically significant. Possible mechanism of this phenomenon is the dominant inhibition of drug transporters in the upper region of the small intestine by AJ. There have been no reports on the localization of OATPs in human intestine and further studies are desirable to elucidate the underlying mechanism of an FEX–AJ interaction to decrease and delay FEX absorption. There were a couple of limitations of the present study. We estimated the effect of various volumes of AJ on FEX exposures primarily based on the changes in AUCs. Data suggested that the elimination patterns were not considerably affected by AJ; however, such data should not be considered conclusive. The last time point of PK sampling (i.e., 11 h post-dose) sufficiently captured the majority of AUC of FEX but not the entire elimination phase, which reportedly persists after 11 h postdose. The possibility of ethnic differences in FEX PK is another limitation of our study. We evaluated the effect of genetic polymorphism of OATP2B1 (SLCO2B1 C3 (1457 C>T), and the AUC of FEX in subjects with a mutant allele (CT or TT) were significantly lower than that in homozygous carriers of the wildtype allele (CC). The participants of the present study were all Japanese, and the minor allele frequency of SLCO2B1 *3 is known to be higher in Japanese (30.9%) than Caucasians (1.2%). Caution should be used before directly generalizing the present results for other ethnic populations, which is an important point to elucidate as a limitation.

In the present study we purposely equalized the total intake volume of AJ and water in each treatment phase where AJ at different volumes was followed by water to make the total intake volume of 600 mL. The total volume of ingested liquid may have a significant effect on absorption of FEX by changing the dissolution profile or delaying gastric emptying time. Therefore, we intended to minimize such effects, but this may also be viewed as a limitation of a controlled laboratory study.

In conclusion, concomitant AJ intake reduces the systemic exposure to FEX in a volume-dependent manner. While a remarkable reduction in FEX AUC is related to large volumes of AJ, the effect of a smaller volume such as 150 mL appeared to be clinically not meaningful when FEX is orally administered with AJ.

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Impact of Apple Juice Volume on Fexofenadine PK
Luo et al.

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