# Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: Possible role of organic anion transporting polypeptides

*Objectives:* **The purpose of this study was to elucidate the potential clinical relevance and mechanism(s) of action of 2 different volumes of grapefruit juice on the reduction of bioavailability of fexofenadine, a substrate of organic anion transporting polypeptides.**

*Methods:* **Grapefruit juice or water at normal (300 mL) or high (1200 mL) volume was ingested concomitantly with 120 mg fexofenadine by 12 healthy volunteers in a randomized 4-way crossover study, and fexofenadine pharmacokinetics were determined over a period of 8 hours.**

*Results:* **The 300-mL volume of grapefruit juice decreased the mean area under the plasma drug concentration–time curve (AUC) and the peak plasma drug concentration of fexofenadine to 58% ($P < .001$) and 53% ($P < .001$), respectively, of those with the corresponding volume of water, and 1200 mL grapefruit juice reduced these parameters to 36% ($P < .001$) and 33% ($P < .001$), respectively, of those with the corresponding volume of water. The 300-mL volume of grapefruit juice diminished the AUC of fexofenadine variably among individuals. This decline correlated with baseline AUC of fexofenadine with water at equivalent volume ($r^2 = 0.97$, $P < .0001$). The 1200-mL volume of grapefruit juice decreased the AUC of fexofenadine more than the 300-mL volume of grapefruit juice compared with the corresponding volume of water in each subject by a constant amount. Grapefruit juice, 300 mL and 1200 mL, reduced the coefficient of variation of the AUC of fexofenadine by 2-fold compared with that with a matching volume of water.**

*Conclusions:* **Grapefruit juice at a commonly consumed volume diminished the oral bioavailability of fexofenadine sufficiently to be pertinent clinically, likely by direct inhibition of uptake by intestinal organic anion transporting polypeptide A (OATP-A; new nomenclature, OATP1A2). A much higher volume caused an additional modest effect, possibly from reduced intestinal concentration and transit time of fexofenadine. This food-drug interaction appears to be novel and may be relevant to other fruit juices and drugs. (Clin Pharmacol Ther 2005;77:170-7.)**

**George K. Dresser, MD, PhD, Richard B. Kim, MD, and David G. Bailey, PhD** *London, Ontario, Canada, and Nashville, Tenn*

Clinical response to an identical dose of a medication can fluctuate substantially within individuals or differ markedly among individuals, resulting in adverse events ranging from lack of efficacy to appearance of toxicity. Because the effect of a drug is most often linked to concentration at the tissue site(s) of action, the outcome of pharmacotherapy can be greatly dependent on the activity of biologic processes that significantly influence the disposition of a drug. Moreover, variability in response within and among individuals is frequently the result of dissimilar activity of these processes, which are com-

From the Lawson Health Research Institute, London Health Sciences Centre, and Departments of Medicine and Physiology and Pharmacology, University of Western Ontario, London, and Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville.

Supported by a grant from the Internal Research Fund of London Health Sciences Centre and US Public Health Service grants GM 31304 and GM 54724.

Presented in part at the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Washington DC, April 2-5, 2003.

Received for publication May 18, 2004; accepted Oct 4, 2004.

Reprint requests: David G. Bailey, PhD, Department of Medicine, London Health Sciences Centre, Victoria Campus, 375 South St, London, Ontario, Canada N6A 4G5.

E-mail: *david.bailey@lhsc.on.ca*

0009-9236/$30.00



doi:10.1016/j.clpt.2004.10.005

monly regulated by environmental or genetic influences. These concepts are relevant and well established for drug-metabolizing enzymes, such as cytochrome P450 (CYP) 3A4, which convert numerous medications to inactive or less active derivatives, and for the efflux transporter P-glycoprotein, which limits intestinal absorption and tissue distribution and facilitates the excretion of many drugs.[1,2]

Recently, molecular cloning and expression experiments with members of the family of drug uptake transporters known as organic anion transporting polypeptides (OATPs) point to the likelihood that they also play a crucial role in drug disposition.[3] In the small intestine, OATPs appear to affect certain orally administered medications by enabling enteric absorption, a key initial step for systemic action of a medication. Consequently, modulation of the activity of intestinal OATPs might be expected to alter the oral bioavailability and subsequent clinical response of a drug.

The latest findings have shown that constituents in the diet reduced the activity of several OATPs.[4] In vitro, substantially diluted concentrations of grapefruit, orange, and apple juices and their specific ingredients were potent inhibitors. In humans, a normal concentration of these juices at a high volume (1200 mL) profoundly decreased the oral bioavailability of the antihistamine fexofenadine, a nonmetabolized substrate of certain OATPs.[4-6]

The purpose of this study was to reveal the potential clinical relevance and mechanism(s) of this interaction by use of grapefruit juice as a representative fruit juice and by assessment of the effect of fluid volume on the single-dose oral pharmacokinetics of fexofenadine. A randomized 4-way crossover study was conducted in which 12 healthy volunteers received grapefruit juice or water at normal (300 mL) or high (1200 mL) volume with 120 mg fexofenadine. The 300-mL volume of grapefruit juice was selected because it represents the usual amount commercially available in individual juice containers in North America and thus has practical clinical relevance, whereas the incorporation of the 1200-mL volume of grapefruit juice in the study served as a reference point to our initial publication, which used this large volume so that a possible effect would not be missed. Results indicated that a routinely consumed volume (300 mL) of grapefruit juice produced a potentially clinically relevant reduction in the oral bioavailability of fexofenadine, likely by a mechanism involving direct inhibition of the inherent activity of intestinal OATP-A (OATP1A2). A much higher volume (1200 mL) of juice caused a moderate additional reduction, possibly from less exposure of fexofenadine to this enteric transporter through diminished intestinal drug concentration or transit time. This food-drug interaction is likely to be original and applicable to other fruit juices and drugs.

## METHODS

***Study population.*** We tested 12 subjects (7 men and 5 women; age range, 23-47 years). They were healthy as determined by medical history, physical examination, and routine hematologic and serum chemical testing. No subject had a significant illness within the preceding 2 weeks, had routinely used prescription or over-the-counter medications, or had a history of cardiac, renal, hepatic, or gastrointestinal disease or drug or alcohol abuse. The Research Ethics Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario (London, Ontario, Canada) approved the study, and all subjects provided written informed consent.

***Experimental protocol.*** The study was a single-dose, randomized, open, 4-way crossover, and controlled clinical investigation. Subjects consumed 300 mL grapefruit juice (Everfresh, Windsor, Ontario, Canada), 300 mL water, 1200 mL grapefruit juice (300 mL grapefruit juice with drug followed by 150 mL every 0.5 hour until 3 hours after dosing), or 1200 mL water (same schedule as for 1200 mL grapefruit juice) with 120 mg fexofenadine (Hoechst Marion Roussel Canada, Inc, Laval, Quebec, Canada). Grapefruit juice was purchased as a single lot in bottles containing 300 mL juice at normal strength, which had been previously reconstituted from concentrate.

Subjects fasted from 10 PM on the evening before testing. Peripheral venous blood (5 mL) was sampled into tubes that contained ethylenediaminetetraacetic acid just before and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, and 8.0 hours after administration of fexofenadine for measurement of plasma drug concentrations. A standardized lunch was provided at 4 hours after dosing. All subjects were asked not to consume citrus products or fruit juices for 1 week before and throughout testing, with the exception of the grapefruit juice provided in the study. They were required to abstain from alcohol and not to take medications including over-the-counter preparations for 48 hours before testing. Tobacco and caffeine-containing beverages were not permitted during testing. The washout period between testing was 1 week. Subjects were asked to maintain a consistent diet throughout all phases of testing.

***Assay of plasma fexofenadine concentration.*** The plasma concentration of fexofenadine was quantified as

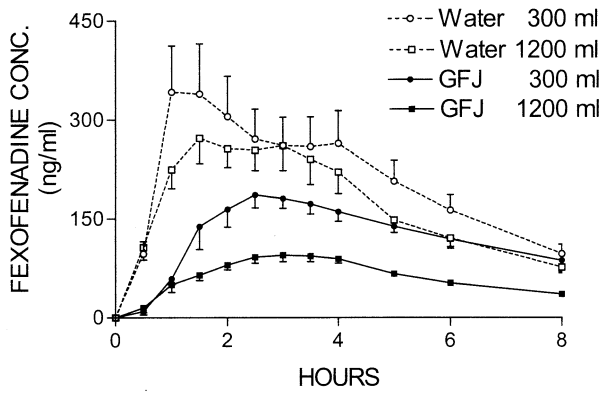


**Fig 1.** Mean plasma drug concentration–time curves of 120 mg fexofenadine for individuals (N = 12) administered water or grapefruit juice (GFJ), 300 mL or 1200 mL (300 mL with drug followed by 150 mL every 0.5 hour until 3.0 hours). *Bars* represent SEM.

outlined previously.[4] A 100-mg C18 preparatory solid-phase extraction column (Sep-Pak Vac cartridge; Waters Corp, Mississauga, Ontario, Canada) was washed with 1-mL volumes of isopropyl alcohol, methanol, and water. A 500-μL aliquot of aqueous 1% phosphoric acid was added, followed by a 500-μL aliquot of the plasma sample for analysis. The mixture was then passed through the column. The column was washed once with a 1-mL volume of aqueous 1% phosphoric acid water, 3 times with a 1-mL volume of water/methanol/glacial acetic acid (88:10:2 [vol/vol]), and 3 times with a 1-mL volume of water/methanol/concentrated ammonium hydroxide (88:10:2 [vol/vol]). The sample was eluted with 1 mL of methanol/triethylamine (99.8:0.2 [vol/vol]), and the effluent was evaporated to dryness at 40°C under a gentle stream of nitrogen. The residue was dissolved in a 100-μL aliquot of HPLC mobile phase that consisted of acetonitrile/water/triethylamine (33:67:1 [vol/vol] at pH 3.0) with phosphoric acid. Recovery of fexofenadine from the solid-phase extraction column was complete. The solution was filtered (0.45 μm), and a sample (40 μL) was injected onto a Prodigy 5-μm octadecylsilane (2) column (150 mm × 3.2 mm; Phenomenex, Torrance, Calif) with a mobile flow rate of 0.4 mL/min. Fluorescence detection (excitation wavelength, 223 nm; emission wavelength, 290 nm) was used to monitor the effluent. The retention time of fexofenadine was 10.9 minutes. The standard curve of fexofenadine was linear over the range of concentrations measured in the plasma samples from the study (0-1000 ng/mL). The coefficient of variation was 4.8% at 25 ng/mL (n = 5), and the limit of detection was 5 ng/mL.

***Data analysis.*** Plasma fexofenadine concentrations were analyzed by use of a noncompartmental model method. The terminal elimination rate constant ($k_e$) was determined by log-linear regression of the final data points (at least 3). The apparent elimination half-life of the log-linear phase ($t_{½}$) was calculated as $0.693/k_e$. The area under the plasma drug concentration–time curve from 0 to 8 hours [AUC(0-8)] was calculated by use of the linear trapezoidal method. The AUC from 8 hours to infinity [AUC(8-∞)] was determined by dividing the final plasma fexofenadine concentration by $k_e$. Peak plasma drug concentration ($C_{max}$) and the time to reach $C_{max}$ ($t_{max}$) were obtained directly from the experimental data.

Statistical comparisons among the 4 treatment groups initially used ANOVA for repeated measures. For those analyses where *P* was less than .05, a priori comparisons were performed between grapefruit juice versus water treatments for 300-mL or 1200-mL volumes and between 300-mL volumes versus 1200-mL volumes for grapefruit juice or water treatments by use of the paired *t* test. Statistical significance was determined by the Bonferroni method by correcting for the number of comparisons (ie, 0.05/4 = 0.0125). The coefficient of variation was expressed as a percent of SD/mean. Data are presented as mean values ± SEM.

## RESULTS

Grapefruit juice, 300 mL or 1200 mL, produced lower mean plasma concentrations, AUC, and $C_{max}$ of fexofenadine compared with the corresponding volume of water (Fig 1 and Table I). The 300-mL volume of grapefruit juice reduced mean AUC and $C_{max}$ of fexofenadine to 58% and 53%, respectively. The 1200-mL volume of grapefruit juice lowered these parameters to 36% and 33%, respectively. Grapefruit juice or water at 300 mL or 1200 mL did not produce different $t_{max}$ or $t_{½}$ of fexofenadine. The 300-mL volume of grapefruit juice had higher mean plasma concentrations, AUC, and $C_{max}$ of fexofenadine than 1200 mL grapefruit juice.

The 300-mL volume of grapefruit juice produced an interindividual reduction in the AUC of fexofenadine that was variable; a greater reduction in the AUC of fexofenadine with 300 mL grapefruit juice occurred with a higher baseline AUC of fexofenadine with an equivalent volume of water (Fig 2). The 1200-mL volume of grapefruit juice caused a moderately larger reduction compared with 300 mL grapefruit juice relative to the corresponding volume of water; this addi-

**Table I.** Plasma pharmacokinetics of 120 mg fexofenadine administered with water or grapefruit juice, 300 mL or 1200 mL (300 mL with drug followed by 150 mL every 0.5 hour until 3.0 hours [total volume of 1200 mL])

| | *Water* | | *Grapefruit juice* | |
|---|---|---|---|---|
| | *300 mL* | *1200 mL* | *300 mL* | *1200 mL* |
| AUC(0-8) (ng · h/mL) | 1685 ± 237 | 1379 ± 155 | 980 ± 68*† | 491 ± 28† |
| AUC(0-∞) (ng · h/mL) | 2167 ± 283 | 1747 ± 184 | 1379 ± 122*† | 677 ± 41† |
| $C_{max}$ (ng/mL) | 436 ± 74 | 326 ± 37 | 233 ± 25*† | 109 ± 8† |
| $t_{max}$ (h) | 2.0 ± 0.4 | 2.1 ± 0.3 | 3.3 ± 0.6 | 2.9 ± 0.4 |
| $t_{½}$ (h) | 3.0 ± 0.5 | 3.2 ± 0.2 | 3.1 ± 0.2 | 3.5 ± 0.2 |

Data are expressed as mean ± SEM.
AUC(0-8), Area under plasma drug concentration–time curve from 0 to 8 hours; AUC(0-∞), area under plasma drug concentration–time curve from 0 hours extrapolated to infinity; $C_{max}$, peak plasma drug concentration; $t_{max}$, time to reach peak plasma drug concentration; $t_{½}$, elimination half-life.
*$P < .01$ for 300 mL versus 1200 mL for water or grapefruit juice.
†$P < .001$ for water versus grapefruit juice for 300 mL or 1200 mL at equivalent volume.

tional interindividual decrease in the AUC of fexofenadine was constant.

The 300-mL volume of water produced mean plasma concentrations and pharmacokinetics of fexofenadine that were not different from those with 1200 mL water. However, 3 individuals with the highest AUC of fexofenadine with 300 mL water had a decrease in this parameter with 1200 mL water (Fig 3).

Both 300 mL and 1200 mL grapefruit juice markedly reduced the variability of the AUC of fexofenadine among individuals compared with the matching volume of water (Fig 4). The 300-mL volume of grapefruit juice had a coefficient of variation of 24% compared with 49% as calculated for 300 mL water. The 1200-mL volume of grapefruit juice had a coefficient of variation of 20% relative to 39% as calculated for 1200 mL water.

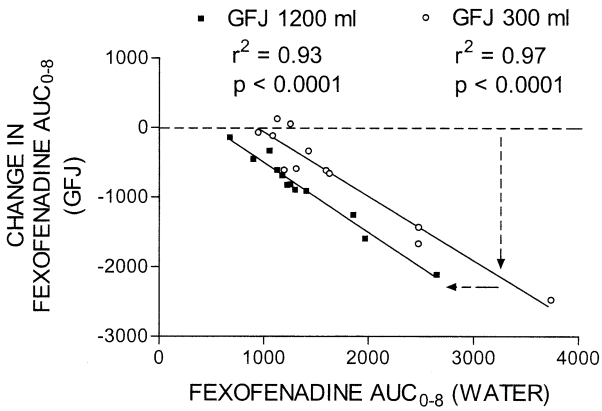


**Fig 2.** Area under plasma drug concentration–time curve from 0 to 8 hours [AUC(0-8)] of 120 mg fexofenadine with water, 300 mL or 1200 mL (300 mL with drug followed by 150 mL every 0.5 hour until 3.0 hours), plotted against absolute change in this parameter with matching volume of GFJ for each individual (N = 12). *Horizontal dashed line* indicates no change in fexofenadine AUC(0-8). The lines of best fit (*solid lines*) were determined by linear regression analysis. *Dashed lines with arrows* indicate the variable and constant components of the interaction.

## DISCUSSION

Because our previous pharmacokinetic interaction study showed that grapefruit juice at a high volume (1200 mL) markedly diminished the oral bioavailability of fexofenadine to 35% of that seen with an equivalent volume of water,[4] it was hypothesized that grapefruit juice at a more commonly used volume (300 mL) would also generate a potentially pertinent outcome. Results showed that 300 mL grapefruit juice lowered the mean oral bioavailability of fexofenadine to 58% compare with 300 mL water. Thus concomitant grapefruit juice at a frequently consumed amount may cause an unwanted decrease or duration of efficacy of fexofenadine. Indeed, the reduction of the administered dose of fexofenadine from 130 mg to 40 mg substantially shortened the duration of clinical efficacy of fexofenadine as measured by the single-dose change in the wheal area–time profile.[7]

Establishing the cause of this interaction necessitated deliberation on major aspects that determine the oral bioavailability of a drug, which requires that the chemically unchanged form of a drug undergo a number of essential sequential events. The drug must undergo dissolution from the tablet matrix, transfer from the stomach to the small intestine, passage through the small intestinal wall into the portal circulation, and then conveyance through the liver.

Because fexofenadine is a zwitterion, it carries an ionic charge and has high aqueous solubility over a

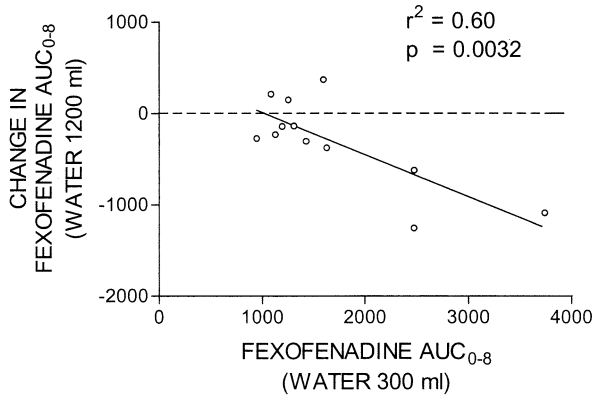


**Fig 3.** AUC(0-8) of 120 mg fexofenadine with 300 mL water plotted against absolute change in this parameter with 1200 mL water (300 mL with drug followed by 150 mL every 0.5 hour until 3.0 hours) for each individual (N = 12). *Horizontal dashed line* indicates no change in fexofenadine AUC(0-8). The line of best fit (*solid line*) was determined by linear regression analysis.

broad pH range. Consequently, it seems unlikely that the acidic pH of grapefruit juice would decrease the dissolution of fexofenadine in the gastrointestinal tract. Moreover, a greater volume of juice might be expected to favor dissolution of fexofenadine. Given that 1200 mL grapefruit juice diminished the oral bioavailability of fexofenadine more than 300 mL grapefruit juice, it seemed unlikely that this juice acted primarily by adversely affecting dissolution of this drug.

Fexofenadine is eliminated essentially unchanged, and the $t_{max}$ values of this drug were similar among treatments.[6] Thus it is doubtful that chemical instability, changed drug metabolism, and altered transit to the intestinal site of absorption were causes for the interaction.

The physicochemical properties of fexofenadine of a high degree of ionization and large polar surface area would predict negligible or low passive intestinal permeability.[8,9] Because this process is traditionally considered to be of primary importance for the passage of drug from the small intestine into the portal circulation, fexofenadine might be envisaged to have minimal or minor intestinal absorption. Moreover, fexofenadine encounters efflux transport by P-glycoprotein in the enterocytes.[5] Yet the absolute oral bioavailability of fexofenadine is estimated to be 33% in humans.[10] Recent findings indicate that there is substantial expression of OATP-A, which enables uptake transport of fexofenadine, on the luminal membrane of human intestinal enterocytes.[11] In addition, OATP-B (OATP2B1) has been noted to be capable of mediating the cellular uptake of fexofenadine and is expressed in the intestine.[12,13] However, we have not been able to show that cells overexpressing OATP-B cause significant uptake transport of fexofenadine (R.B.K., unpublished data, September 2004). Although it is possible that both OATP-A and OATP-B may play a role in fexofenadine absorption from the intestine, OATP-A appears to have far greater affinity for fexofenadine and is most likely the major determinant of the extent of absorption of fexofenadine into the portal circulation.

In the liver, OATPs are expressed on the sinusoidal membrane of hepatocytes.[3] However, the OATP-A isoform has not been detected there. P-glycoprotein is located on the bile canalicular membrane. Given that biliary secretion is a major route for elimination of fexofenadine, this might reflect the cooperative action of another OATP isoform plus P-glycoprotein. However, verapamil and ketoconazole, potent inhibitors of P-glycoprotein, noticeably enhanced the systemic availability of fexofenadine apparently by selectively impairing biliary excretion.[14,15] Thus the biliary excretion of fexofenadine might be mainly dependent on efflux transport mediated by P-glycoprotein.

In this investigation, grapefruit juice decreased the AUC and $C_{max}$ but did not affect the $t_{max}$ or elimination $t_{½}$ of fexofenadine. These data comprise the primary rationale for concluding that the interaction resulted from limiting oral drug bioavailability. In vitro, grapefruit juice at only 0.5% normal strength decreased OATP-A–mediated cellular uptake transport of fexofenadine by half.[4] In contrast, grapefruit juice at 10-fold higher concentration had no effect on cellular monolayer P-glycoprotein–mediated efflux transport of digoxin. This highly potent and selective effect by grapefruit juice on the activity of OATP-A might be the key to understanding the mechanism of this interaction clinically. Given that inhibition of hepatic OATP-mediated fexofenadine uptake would be expected to enhance plasma concentrations of this drug, the most compelling explanation for the mechanism of this interaction is primarily reduction in the amount of fexofenadine undergoing active uptake transport mediated by intestinal OATP-A.

The quantity of fexofenadine that is normally intestinally absorbed might depend on the inherent activity of OATP-A. Given that variability is an intrinsic property of biologic systems, it might be expected that the activity of intestinal OATP-A transporter would range substantially among individuals. Low innate activity might be expected to produce a small AUC for fexofenadine. Conversely, high innate activity might be

envisaged to cause an opposite outcome. Moreover, inhibition of low activity would be predicted to produce less effect than inhibition of high activity. Given that the 4-fold variation of baseline AUC of fexofenadine with water strongly inversely correlated with the diminution of this parameter with grapefruit juice among individuals, the interaction is consistent with an effect on innate intestinal OATP-A. In addition, specific constituents in grapefruit juice including the furanocoumarins bergamottin and 6′,7′-dihydroxybergamottin and the bioflavonoid naringin are normally present in this juice at concentrations that are 5-, 8-, and 150-fold higher, respectively, than those shown to cause at least 50% inhibition of in vitro activity of oatp3, the rat intestinal ortholog of human OATP-A.[4,16] Thus data from 2 sources point to 1 or more specific ingredients in grapefruit juice directly inhibiting the inherent activity of intestinal OATP-A as one basis for the pharmacokinetic interaction.

Recent findings show that 300 mL grapefruit juice can lower the AUC and $C_{max}$ of fexofenadine even when juice is consumed 2 hours before administration of this drug.[17] The magnitude of reduction was essentially the same as that with concomitant ingestion of juice. Given that simultaneous consumption of grapefruit juice produced a $t_{max}$ of fexofenadine of 2.2 ± 0.2 hours (mean ± SEM), it appears unlikely that grapefruit juice would be left in the stomach at this time. Furthermore, ingestion of juice 2 hours earlier would most likely result in a negligible amount remaining in the small intestine at the time of peak absorption of fexofenadine. Data from other sources reported that the clearance of saline solution and 25% dextrose from the stomach ranged from 30 to 90 minutes.[18-20] Thus results indicate that specific ingredients in grapefruit juice might have residual inhibitory action on the activity of enteric OATP-A.

Grapefruit juice is known to cause prolonged inhibition of intestinal drug metabolism mediated by CYP3A4.[21-24] Furanocoumarins in grapefruit juice are considered to be metabolized by CYP3A4 in vivo to reactive intermediates that then bond covalently and irreversibly inactivate this enzyme, a process termed *suicide* or *mechanism-based inhibition*.[25-34] Moreover, these same furanocoumarins can inhibit in vitro activities of oatp3.[4] Consequently, reactive intermediates may inactivate both CYP3A4 and OATP-A in enterocytes. Altered trafficking of enteric OATP-A from the membrane into the cytosol might also occur. Either mechanism might explain the residual effect of grapefruit juice on the oral absorption of fexofenadine and require testing.

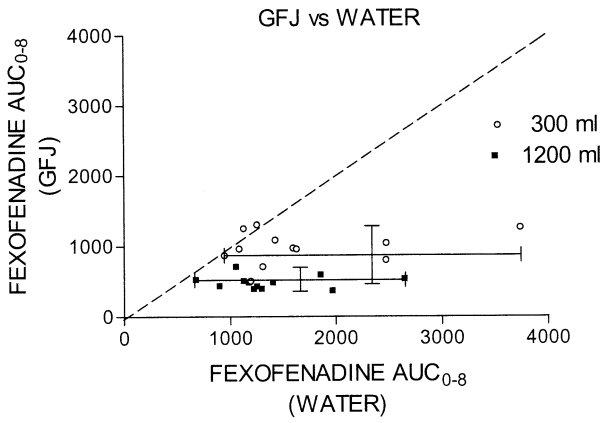


**Fig 4.** AUC(0-8) of 120 mg fexofenadine with water, 300 mL or 1200 mL (300 mL with drug followed by 150 mL every 0.5 hour until 3.0 hours), plotted against same parameter with matching volume of GFJ for each individual (N = 12). The *solid lines with end brackets* indicate the observed range of values for each treatment. The *dashed line* is the line of identity.

Two substantially different volumes of grapefruit juice were tested, and dissimilar quantitative responses were observed. The 300-mL and 1200-mL volumes of grapefruit juice diminished the mean oral bioavailability of fexofenadine to 58% and 36% of those observed with equivalent volumes of water, respectively. Given that a 4-fold higher volume of grapefruit juice reduced the AUC of fexofenadine only moderately more, 300 mL grapefruit juice may be near the upper portion of the volume-response curve. Consequently, a volume of grapefruit juice of less than 300 mL may also bring about a clinically relevant reduction in the oral bioavailability of fexofenadine.

The 300-mL volume of grapefruit juice created an interindividual decrease in the AUC of fexofenadine that was variable. The 1200-mL volume of grapefruit juice resulted in an additional reduction that was constant. These divergent responses may reflect dissimilar mechanisms. The smaller volume of grapefruit juice brought about the majority of the effect, probably by near-maximum direct inhibition of the intrinsic activity of intestinal OATP-A. The substantially higher volume of juice added a supplementary smaller effect. Moreover, certain individuals who initially absorbed fexofenadine well with 300 mL water had a decline in the oral bioavailability of fexofenadine with 1200 mL water. Thus the 1200-mL volume containing more solutes (nonabsorbed carbohydrates or salts) and osmotic effects or just more fluid might decrease intestinal con-

centration or transit time of drug. Under linear transport kinetics, a diminution of either of these parameters would be calculated to cause a proportional decline in the amount of fexofenadine undergoing intestinal uptake transport. Thus it seems reasonable to speculate that markedly additional fluid in the gastrointestinal tract, whether through more solutes and enhanced osmotic effect or simply greater intake of total volume, might diminish the concentration or transit time of fexofenadine sufficiently to affect the intestinal absorption of this drug adversely.

Grapefruit juice halved the coefficient of variation in the AUC of fexofenadine among individuals compared with the equivalent volume of water. Despite the understandable disadvantage of an observed reduction in the oral bioavailability of a drug, the better reliability of this parameter with grapefruit juice may improve the dose-response relationship of fexofenadine among and within individuals. In other words, it may make the effect of a drug more predictable. This approach may have some application for medications that have variable oral pharmacokinetics and a narrow range of plasma concentrations between therapeutic efficacy and toxicity. For example, grapefruit juice has been shown to produce a relevant decrease in the plasma concentrations of the chemotherapeutic agent etoposide.[35] If the mechanism of this interaction with etoposide were found to be inhibition of intestinal OATP-A, this approach might have some practical value. However, a reduction in the coefficient of variation of the AUC of fexofenadine by grapefruit juice may not be a consistent finding.[4] Consequently, additional research would need to be conducted.

In conclusion, a commonly consumed volume (300 mL) of grapefruit juice produced a diminution of oral bioavailability of the drug probe fexofenadine of sufficient magnitude to be pertinent clinically, potentially resulting in reduced benefit of drug. The mechanism appeared to be unique. The most convincing explanation was that this volume of grapefruit juice contained sufficient specific active ingredients to produce a direct and prolonged inhibitory effect on inherent activity of intestinal OATP-A. Because it caused a near-maximum reduction in the amount of fexofenadine undergoing active uptake transport, a marked interaction may be apparent also at a lower volume of this juice. Ingestion of a markedly higher quantity (1200 mL) of grapefruit juice brought about a modest additional effect, possibly as a result of a mechanism involving lessened exposure of fexofenadine to intestinal OATP-A through reduced concentration and transit time of drug in the gastrointestinal tract. Despite decreased systemic availability, grapefruit juice created a more standard relationship between dose and oral bioavailability of fexofenadine in this study, supporting the importance of enteric OATP-A as a determinant of the variability of oral bioavailability of fexofenadine among subjects and suggesting an approach to obtain a more predictable clinical effect for drugs possessing a narrow therapeutic index.

None of the authors has any financial or other relationships that could lead to conflicts of interest.

### *References*

1. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38:41-57.
2. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003;42:59-98.
3. Kim RB. Transporters and drug disposition. Curr Opin Drug Discov Deliv 2000;3:94-101.
4. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman D, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002;71:11-20.
5. Cvetkovic M, Leak B, Fromm MF, Wilkinson GR, Kim RB. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. Drug Metab Dispos 1999;27:866-71.
6. Lippert C, Ling J, Brown P, Burmaster S, Eller M, Cheng L, et al. Mass balance and pharmacokinetics of MDL 16455A in healthy male volunteers [abstract]. Pharm Res 1995;12:S-390.
7. Russell T, Stoltz M, Weir S. Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. Clin Pharmacol Ther 1998;64:612-21.
8. Winiwarter S, Bonham NM, Ax F, Hallberg A, Lennernas H, Karlen A. Correlation of jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. J Med Chem 1998;41:4939-49.
9. Kelder J, Grootenhuis PD, Bayada DM, Delbressine LP, Ploemen JP. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. Pharm Res 1999;16:1514-9.
10. Fexofenadine [product information]. Laval, Quebec (Canada): Hoechst Marion Roussel Canada, Inc.
11. Smith LH, Lee W, Kim RB. Differential expression of OATP drug uptake transporters in human liver, intestine, and kidney [abstract]. Drug Metab Rev 2003;35:73.
12. Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Functional characterization of pH-sensitive organic anion transport-

ing polypeptide OATP-B in humans. J Pharmacol Exp Ther 2004;308:438-45.
13. Kullak-Ublick GA, Ismair MG, Stieger B, Landmann L, Huber R, Pizzagalli F, et al. Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. Gastroenterology 2001;120:525-33.
14. Tannergren C, Petri N, Knutson L, Hedeland M, Bondesson U, Lennernas H. Multiple transport mechanisms involved in the intestinal absorption and first-pass extraction of fexofenadine. Clin Pharmacol Ther 2003;74:423-36.
15. Tannergren C, Knutson T, Knutson L, Lennernas H. The effect of ketoconazole on the in vivo intestinal permeability of fexofenadine using a regional perfusion technique. Br J Clin Pharmacol 2003;55:182-90.
16. Walters HC, Craddock AL, Fusegawa H, Willingham MC, Dawson PA. Expression, transport properties, and chromosomal location of organic anion transporter subtype 3. Am J Physiol Gastrointest Liver Physiol 2000; 279:G1188-200.
17. Dresser GK, Kim RB, Bailey DG. Duration of grapefruit juice effect on fexofenadine interaction [abstract]. Clin Pharmacol Ther 2003;73:P48.
18. Collins PJ, Houghton LA, Read NW, Horowitz M, Chatterton BE, Heddle R, et al. Role of the proximal and distal stomach in mixed solid and liquid meal emptying. Gut 1991;32:615-9.
19. Husebye E. The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. Neurogastroenterol Motil 1999;11:141-61.
20. Ouyang A, Sunshine AG, Reynolds. Caloric content of a meal affects duration but not contractile pattern of duodenal motility in man. Dig Dis Sci 1989;34:528-36.
21. Lundahl J, Regardh CG, Edgar B, Johnsson G. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. Eur J Clin Pharmacol 1995;49:61-7.
22. Takanaga H, Ohnishi A, Murakami H, Matsuo H, Higuchi S, Urae A, et al. Relationship between time after intake of grapefruit juice and the effect on the pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. Clin Pharmacol Ther 2000;67:201-14.
23. Lilja JJ, Kivisto KT, Neuvonen PJ. Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. Clin Pharmacol Ther 2000;68:384-90.
24. Greenblatt DJ, von Moltke LL, Harmatz JS, Chen G, Weemhoff JL, Jen C, et al. Time course of recovery of cytochrome P450 3A function after single doses of grapefruit juice. Clin Pharmacol Ther 2003;74:121-9.
25. Bailey DG, Dresser GK, Kreeft JH, Munoz C, Freeman DJ, Bend JR. Grapefruit-felodipine interaction: effect of unprocessed fruit and probable active ingredients. Clin Pharmacol Ther 2000;68:468-77.
26. Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545-53.
27. Edwards DJ, Bellevue FH, Woster PM. Identification of 6′,7′-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice. Drug Metab Dispos 1996;24: 1287-90.
28. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, He K, Lown KS, Woster PM, et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents. Decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. Drug Metab Dispos 1997;25:1228-33.
29. Fukuda K, Ohta T, Oshima Y, Ohashi N, Yoshikawa M, Yamazoe Y. Specific CYP3A4 inhibitors in grapefruit juice: furocoumarin dimers as components of drug interaction. Pharmacogenetics 1997;7:391-6.
30. He K, Iyer KR, Hayes RN, Sinz MW, Woolf TF, Hollenberg PF. Inactivation of cytochrome P450 3A4 by bergamottin, a component of grapefruit juice. Chem Res Toxicol 1998;11:252-9.
31. Ohnishi A, Matsuo H, Yamada S, Takanaga H, Morimoto S, Shoyama Y, et al. Effect of furanocoumarin derivatives in grapefruit juice on the uptake of vinblastine by Caco-2 cells and on the activity of cytochrome P450 3A4. Br J Pharmacol 2000;130:1369-77.
32. Tassaneeyakul W, Guo LQ, Fukuda K, Ohta T, Yamazoe Y. Inhibition selectivity of grapefruit juice components on human cytochromes P450. Arch Biochem Biophys 2000;378:356-63.
33. Guo LQ, Fukuda K, Ohta T, Yamazoe Y. Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. Drug Metab Dispos 2000;28:766-71.
34. Ohta T, Nagahashi M, Hosoi S, Tsukamoto S. Dihydroxybergamottin caproate as a potent and stable CYP3A4 inhibitor. Bioorg Med Chem 2002;10:969-73.
35. Reif S, Nicolson MC, Bisset D, Reid M, Kloft C, Jaehde U, et al. Effect of grapefruit juice intake on etoposide bioavailability. Eur J Clin Pharmacol 2002;58:491-4.