

NOTES

Effect of Grapefruit Juice on Clarithromycin Pharmacokinetics

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To investigate whether grapefruit juice inhibits the metabolism of clarithromycin, 12 healthy subjects were given water or grapefruit juice before and after a clarithromycin dose of 500 mg in a randomized crossover study. Administration of grapefruit juice increased the time to peak concentration of both clarithromycin (82 ± 35 versus 148 ± 83 min; $P = 0.02$) and 14-hydroxyclearithromycin (84 ± 38 min versus 173 ± 85 ; $P = 0.01$) but did not affect other pharmacokinetic parameters.

Grapefruit juice has been shown to increase the maximum concentration (C_{max}), area under the curve (AUC), and bioavailability of certain orally administered medications that are metabolized by cytochrome P-450 3A4 (CYP3A4) (1, 7, 13-17, 20). This interaction is postulated to occur by inhibition of CYP3A4 enzymes at the gut wall, since comparative studies between oral and intravenous forms of medications have shown that grapefruit juice affects the pharmacokinetics of only the oral dosage forms (7, 15, 21). Clarithromycin is a macrolide antibiotic which is metabolized by the CYP3A4 enzyme system to an active metabolite, 14-hydroxyclearithromycin (14-OH-C), and other, inactive metabolites (2). It has been anecdotally recommended that patients take clarithromycin with grapefruit juice to decrease the metallic taste that may be experienced with the medication. In addition, grapefruit juice may affect the pharmacokinetics of medications metabolized by CYP3A4 enzymes even when it is not concurrently ingested with the medication. Lundahl et al. (16) showed that felodipine pharmacokinetics were affected even when administered up to 24 h after grapefruit juice ingestion. The high potential for grapefruit juice to be consumed with clarithromycin and the possibility that grapefruit juice need not be concurrently administered with medications to affect their pharmacokinetics warrant the need to look into a possible drug-food interaction. The purpose of this study was to determine whether grapefruit juice affects the pharmacokinetics of clarithromycin or its active metabolite, 14-OH-C.

This protocol was approved by the Institutional Review Board of Bassett Healthcare. A power calculation using an α level of 0.05, a β level of 0.10, and an estimated clinically significant 25% reduction in the test group indicated that a sample size of 12 individuals was necessary to find a difference. The needed 12 subjects (six males and six premenopausal females; ages, 35.3 ± 7 years; total body weight, 69.8 ± 11 kg; calculated creatinine clearance, 85.9 ± 11 ml/min/1.73 m² [5]) were enrolled. All subjects provided written, informed consent and were healthy as determined by medical history, physical

exam, and laboratory screening (a complete blood count, serum chemistries, urinalysis, and serum pregnancy tests in women of childbearing potential). Subjects were at least 19 years of age and free of any drug exposure except for acetaminophen for at least 10 days prior to the study period. Exclusion criteria included a sensitivity to macrolide antibiotics or intolerance of any other medication; history of blood dyscrasias; recent history of drug or alcohol abuse; use of astemizole 30 days prior to the study; use of terfenadine or loratadine 14 days prior to the study; and utilization of nicotine delivery systems in the past 12 months. All screening blood work was repeated after the last phase of the study to document any laboratory-induced adverse effects.

This was an open-labeled, randomized, crossover study. A random number table (6) was used to assign subjects to an initial treatment phase in a 1:1 allocation. After an overnight fast of at least 8 h, subjects were randomized to receive a single oral dose of 500 mg of clarithromycin with 240 ml of either water or freshly squeezed white grapefruit juice at time zero and 2 h after clarithromycin administration. Food was withheld until 4 h after clarithromycin administration. No alcohol or caffeine was allowed during the study. Subjects were instructed to avoid citrus beverages, citrus fruits, cruciferous vegetables, charbroiled meats, and fatty foods during the study period. The washout period between the treatment phases was 7 days. Blood was sampled prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 48, and 72 h after clarithromycin administration. After centrifugation, serum samples were stored at -80°C until assayed. Concentrations of clarithromycin and 14-OH-C in serum were assayed with a validated high-pressure liquid chromatography (HPLC) assay. The HPLC assay was performed with a Waters model 510 pump and model 680 gradient controller and solvent select valve, a Spectra Physics model 8875 fixed-volume autosampler, an ESA Coulochem II electrochemical detector, a Macintosh 7100 computer, and the Rainin Dynamax HPLC data management system. The serum standard curves for clarithromycin and 14-OH-C ranged from 0.20 to 10.00 mg/liter and 0.18 to 4.42 mg/liter, respectively. The fits of the standard curves were achieved by using a weighting scheme of $1/y^2$. The coefficients of determination for the standard curves all exceeded 0.998. The recovery of clarithromycin from serum was 101.1% (range, 98.3 to 103.3%). Testing for clarithromycin within-sample precision produced a

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TABLE 1. Pharmacokinetics of clarithromycin and 14-OH-C when administered with water or grapefruit juice^a

Treatment phase	C_{\max} ($\mu\text{g/ml}$)	T_{\max} (min) ^b	k_{el} (min^{-1})	$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{min/ml}$)	CL_t/F (ml/min)	$t_{1/2}$ (min)
Clarithromycin						
Water	2.4 \pm 0.8	82.2 \pm 35.2	2.6 \pm 0.7	1,202.2 \pm 552.5	523.6 \pm 292.4	278.8 \pm 64.2
Grapefruit	2.5 \pm 0.9	148.1 \pm 83.0*	2.6 \pm 0.7	1,382.1 \pm 556.0	444.8 \pm 261.3	289.3 \pm 76.2
14-OH-C						
Water	1.2 \pm 0.4	83.5 \pm 38.0	1.9 \pm 0.5	817.6 \pm 259.7	667.3 \pm 197.7	382.9 \pm 94.8
Grapefruit	1.0 \pm 0.3	172.7 \pm 84.7**	1.7 \pm 0.6	833.2 \pm 199.4	629.8 \pm 138.8	453.2 \pm 157.2

^a A 500-mg oral dose of clarithromycin was used. Data are means \pm standard deviations.

^b * and **, $P \leq 0.05$ and 0.005 , respectively, compared with control value.

coefficient of variation of 1.9%. Testing for clarithromycin day-to-day assay precision produced a coefficient of variation of 3.7% (low of 0.9% at 5.0 mg/liter, high of 7.5% at 0.5 mg/liter). Similar parameters were determined for 14-OH-C.

Serum clarithromycin and 14-OH-C data were modeled via noncompartmental analysis using TOPFIT version 2.0 (19) and a weighting scheme of $1/y^2$. Parameters obtained from the analysis included C_{\max} , time to peak concentration (T_{\max}), AUC from 0 h to infinity ($\text{AUC}_{0-\infty}$), half-life ($t_{1/2}$), total oral clearance (CL_t/F , where F is bioavailability), and elimination rate constant (k_{el}). After verification of normality for all pharmacokinetic parameters via proc univariate analyses, the paired Student t test was applied to make statistical comparisons between clarithromycin and 14-OH-C pharmacokinetics during the treatment phases with the Statistical Analysis System (SAS, Cary, N.C.). Significance was defined as a P value of ≤ 0.05 . Data are presented as means \pm standard deviations.

All study subjects completed the study. The adverse effects experienced by subjects were comparable to those experienced in previous clarithromycin studies with mild gastrointestinal upset and taste perversion being the most common (3, 4). In the control arm, 25% of subjects experienced gastrointestinal upset (i.e. diarrhea, abdominal cramps, and gas) versus 8.3% in the grapefruit juice arm. In addition, 33% of subjects in the control arm experienced taste perversions compared to 16.6% in the grapefruit juice arm. Events were mild and unrelated to age or sex of subjects. Though interesting, these differences were not statistically significant. Compared to water, grapefruit juice significantly delayed the T_{\max} of both clarithromycin (82.2 \pm 35 versus 148.1 \pm 83 min, respectively; $P = 0.02$) and 14-OH-C (84.5 \pm 38 versus 172.7 \pm 85 min, respectively; $P = 0.01$). However, grapefruit juice failed to produce any significant effect on other pharmacokinetic parameters (Table 1).

According to this study, freshly squeezed white grapefruit juice did not affect the extent of absorption of clarithromycin. It also did not affect the metabolism of clarithromycin, as the C_{\max} and AUC values of 14-OH-C did not differ significantly between treatment phases. The minor changes that were identified most likely represent a mild interaction, but the study was underpowered to appropriately identify their significance. White grapefruit juice did delay the T_{\max} of both clarithromycin and 14-OH-C, and this can probably be explained as a delay in the absorption of clarithromycin. Though unlikely to be due to a delay in gastric emptying, this may represent competition for intestinal CYP3A4 and/or absorptive sites. An hour-long delay in the appearance of clarithromycin and 14-OH-C in serum is probably not clinically significant, since clarithromycin and 14-OH-C have $t_{1/2}$ s of 5 to 7 h and 8 to 12 h, respectively (4). With twice-daily dosing, therapeutic concentrations of clarithromycin and 14-OH-C in serum would be maintained.

The methods, materials, and design of this study were sim-

ilar to those used in most other grapefruit juice studies that have identified significant interactions with other medications. The amount of grapefruit juice administered to the subjects in this study was comparable to the amount administered in studies that found significant changes in the pharmacokinetics of other medications (13, 17). Like most of the published grapefruit juice-drug interaction studies, this study did not attempt to quantitate any component of the freshly squeezed white grapefruit juice that was administered to our subjects. Past studies and reviews have implicated flavonoids, namely, naringin, as the cause of CYP3A4 inhibition (2, 11). While naringin has little inhibitory activity on CYP3A4 enzymes, conversion to its metabolite naringenin is key to having significant enzyme inhibition. This may explain the variable effects of grapefruit juice on the pharmacokinetics of medications, since metabolism of naringin to naringenin may vary in different individuals and there may also be intraindividual variability (2). Vanakowski et al. (20) quantitated the amount of naringin in the grapefruit juice used in their study, but it is still debatable whether naringin is the active component that is responsible for CYP3A4 enzyme inhibition in the gut. It is postulated that the CYP3A4 gut inhibition is not due to a flavonoid but is instead due to 6',7'-dihydroxybergamottin (8). In the study by Edwards et al. (8), 6',7'-dihydroxybergamottin was isolated from frozen white grapefruit juice concentrate. When 6',7'-dihydroxybergamottin was separated from grapefruit juice, it was found that the juice lacked significant in vitro inhibition of testosterone metabolism in an animal model. With the cause of enzyme inhibition from grapefruit juice still unknown, there has been a lack of standardization in the type of grapefruit juice utilized in grapefruit juice-drug interaction studies. Previous studies have used various types of grapefruit juice. Some trials have used frozen concentrate of white grapefruit juice at regular strength and some at double strength from various manufacturers. It was decided to use freshly squeezed grapefruit juice in this study to avoid the possibility of the manufacturing process destroying or diluting any active component in the juice. Because of this, a more pronounced drug-food interaction would have been expected if grapefruit juice did have an effect on clarithromycin pharmacokinetics.

In other studies, medications such as felodipine ($F = 5$ to 10%) and cyclosporine ($F = 10$ to 60%) that have demonstrated a significant grapefruit juice-drug interaction had low or variable bioavailability (2, 12). In contrast, clarithromycin has a bioavailability of 55%, which may indicate that it undergoes less extensive first-pass metabolism than felodipine or cyclosporine and may explain why grapefruit juice does not significantly affect its pharmacokinetics.

Most community-acquired pathogens, such as *Streptococcus pneumoniae*, are sensitive to clarithromycin at concentrations lower than 2 mg/liter (9). While 14-OH-C has activity against

most bacteria similar to that of clarithromycin, 14-OH-C is twice as active in the treatment of *Haemophilus influenzae* (10, 18). While grapefruit juice has been shown to affect the pharmacokinetics of various medications metabolized by CYP3A4, the current study indicates that freshly squeezed white grapefruit juice does not affect the metabolism of clarithromycin to 14-OH-C. Therefore, it can probably be consumed with clarithromycin to decrease taste perversions without concern that the drug's antimicrobial activity may be altered.

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