Effects of Grapefruit and Seville Orange Juices on the Pharmacokinetic Properties of Colchicine in Healthy Subjects

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ABSTRACT

Background: The labeling for colchicine (indicated for acute gout flares or prophylaxis) includes strict advisories regarding drug–drug and drug–food interactions, including warnings against consuming grapefruit or grapefruit juice during treatment. Two of the furocoumarins in grapefruit juice and Seville orange juice can inhibit intestinal cytochrome P450 (CYP) isozyme 3A4 and P-glycoprotein (involved in colchicine metabolism and transport). Severe toxicities in patients consuming these juices while taking other drugs metabolized through these pathways have been reported.

Objective: Two Phase I studies assessed the effects of multiple daily consumptions of Seville orange juice or grapefruit juice on the pharmacokinetic properties of colchicine in healthy volunteers.

Methods: Healthy volunteers were enrolled in 2 open-label, Phase I studies. Undiluted juice (240 mL) was administered twice daily for 4 days. Pharmacokinetic data were obtained following a single 0.6-mg dose of colchicine before the administration of juice and again following a single 0.6-mg dose of colchicine on the final day of juice administration. In each study, blood samples for pharmacokinetics were collected before dosing with colchicine and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. All subjects were monitored for adverse events (AEs) throughout the confinement portion of the study and were queried at the outpatient visits. AEs were coded according to corresponding MedDRA-coded system organ classes.

Results: Forty-four subjects received either grapefruit juice (72.7% male; 90.9% white) or Seville orange juice (62.5% female; 100% white). Although it is considered to be a moderate concentration-dependent CYP3A4 inhibitor, grapefruit juice did not significantly affect the pharmacokinetic parameters of colchicine. When colchicine was administered with Seville orange juice, a moderate inhibitor, C_{max} and AUC were decreased by ~24% and ~20%, respectively. Seville orange juice also caused, on average, a 1-hour delay in T_{max}. Colchicine in combination with grapefruit or Seville orange juice was well tolerated. There were no significant treatment-related AEs reported, and the most likely AEs were general gastrointestinal events.

Conclusions: In contrast to label warnings based on the literature, grapefruit juice did not affect the pharmacokinetics of colchicine. Seville orange juice paradoxically reduced absorption of colchicine and increased T_{max}, but the clinical significance of this is unknown. Contrary to the expected effects of inhibiting the enzymes that metabolize colchicine, neither juice increased exposure to colchicine. However, the absence of a positive control in these studies dictates that caution should be used when applying these results clinically. ClinicalTrials.gov identifiers: NCT00960193 and NCT00984009. (*Clin Ther.* 2012;34:2161–2173)

Key words: colchicine, drug interaction, grapefruit juice, pharmacokinetics, Seville orange juice.

INTRODUCTION

Consumption of citrus products in the United States is common, and grapefruit is consumed for its health benefits as a citrus fruit that is low in calories and rich in vitamin C, potassium, and dietary fiber. The potential for grapefruit juice to interact with medications

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was first discovered in 1989.[1] It was subsequently reported that healthy subjects who took the calcium channel antagonist felodipine with grapefruit juice had higher felodipine plasma concentrations than did those who took the drug with water; the higher plasma felodipine concentrations resulted in a more pronounced effect of felodipine in terms of decreased blood pressure and other untoward effects after ingesting as little as a single 240-mL glass of grapefruit juice.[2] It has since been established and well documented in the published literature that grapefruit juice is a mechanism-based inhibitor of intestinal, and not hepatic, cytochrome P450 (CYP) 3A4 isozyme (intestinal first-pass metabolism).[3] Grapefruit juice can cause increases in oral bioavailability and prolongation in the elimination half-life of a wide range of other drugs that are CYP3A4 substrates, which can result in increased systemic drug exposure (for recent reviews, see Seden et al,[4] Won et al,[5] and Hanley et al[6]). It has also been reported that Seville orange juice has the same potential as does grapefruit juice for causing food–drug interactions due to the inhibition of intestinal CYP3A4.[7] Both grapefruit juice and Seville orange juice contain furocoumarins, of which bergamottin and 6′,7′-dihydroxybergamottin are the main constituents and are presumed to be the primary compounds effecting CYP3A4 inhibition.[7] Both grapefruit and Seville oranges are believed to be hybrids of pomelo (pummello),[8] the juice of which also contains furocoumarins at concentrations similar to those in grapefruit juice.[9] Medications metabolized by intestinal CYP3A4 enzyme have either a low oral bioavailability or are known to be narrow therapeutic index drugs and are more likely to have clinically significant interactions when coadministered with grapefruit juice and/or Seville orange juice.

Gout, once viewed as a condition of wealthy, overindulging, overweight men, now affects >8.3 million Americans (3.9% of the adult population).[10] Gout is a painful and progressive disease that, if inadequately treated, may lead to joint destruction and deformity, with severely compromised quality of life. In most patients experiencing a flare, recurrent flares are likely and, if untreated, are associated with an increased frequency and severity of flares.[11] The increase in the prevalence of gout has been linked to increased longevity (urate levels rise with age) and unhealthy dietary and lifestyle trends.[12] The prevalences of associated comorbidities, including obesity, hypertension, metabolic syndrome, and type 2 diabetes mellitus, have also increased. Therefore, patients with gout often have a number of other concomitant conditions that also require medications.

Colchicine is a substrate of P-glycoprotein (P-gp),[13] a key protein involved in the multidrug resistance (MDR-1) transport system located in the cell membranes of numerous tissues, and is excreted by both renal and hepatic mechanisms involving P-gp efflux of colchicine across membranes.[14,15] P-gp also plays a role in the known incomplete absorption of colchicine (mean absolute bioavailability, ~45%).[16] P-gp–mediated secretion into the intestine and reabsorption/biliary recirculation occur, as evidenced by secondary peak plasma concentrations and the excretion of parent colchicine in feces.[16–18] Absorbed colchicine is metabolized to a lesser extent (<5%) into inactive oxidative metabolites by intestinal and hepatic CYP3A4.[17,18]

Colchicine, used for >200 years to treat acute gout flares, plays a pivotal role in both the treatment of gout flares as well as long-term prophylaxis. The approved dosing regimen for acute gout attacks requires a single dose of 1.2 mg to be taken immediately on the first signs of an acute flare, followed by a 0.6-mg dose 1 hour later, and the regimen for prophylaxis is 0.6 mg once or twice daily.

Colchicine is generally well tolerated when used at low doses, although its therapeutic index is relatively narrow. Any interaction that results in increased plasma colchicine concentrations can potentially lead to toxicity that may be severe and dangerous. One established cause of severe colchicine-induced toxicity is the coadministration of colchicine with other drugs that inhibit the metabolism of colchicine. Patients with gout are often obese and/or have various comorbidities (eg, renal impairment, metabolic syndrome, diabetes mellitus, dyslipidemia, cardiovascular disease) that require medical treatment with other modalities,[19–21] which can increase the risk for drug–drug interactions. The US Food and Drug Administration (FDA) Adverse Event Reporting System database has reported that when colchicine is coadministered with certain P-gp or CYP3A4 inhibitors, the risk for serious adverse events (AEs), including fatalities and life-threatening conditions, is increased.[22]

As a part of the colchicine drug-development program to identify other coadministered drugs and foods that may alter colchicine concentrations, and to further

provide clinicians with improved prescribing information in the product labeling, a series of drug–drug and food–drug interaction studies have been conducted by the only manufacturer of FDA-approved colchicine. The intent was to provide clear colchicine dose-adjustment guidelines to be used in patients in whom colchicine is combined with various CYP3A4 enzyme and/or P-gp transport inhibitors.[23] Two food–drug interaction studies were included in this program; each evaluated the effects of multiple daily consumptions of grapefruit juice or Seville orange juice on the pharmacokinetic properties of a single 0.6-mg oral dose of colchicine in healthy adult volunteers. The results of these 2 studies are reported here.

METHODS

The 2 separate studies—study 1 (grapefruit juice) and study 2 (Seville orange juice)—followed similar protocols. The primary objective of each study was to determine the effects of multiple daily consumptions of grapefruit juice or Seville orange juice (240 mL twice daily for 4 consecutive days) on the pharmacokinetic properties of a single 0.6-mg oral dose of colchicine administered to healthy adult subjects under fasting conditions. The secondary objective of each study was to assess the tolerability of a single 0.6-mg oral dose of colchicine administered with and without multiple daily consumptions of grapefruit juice or Seville orange juice.

An extraction procedure using solid-phase extraction and analysis of the extract by liquid chromatography-tandem mass spectrometry (LC-MS/MS) was developed and validated for the determination of colchicine in human plasma containing K_2-EDTA as the anticoagulant. The standard curve ranged from 0.2000 to 40.00 ng/mL. Standards and quality control (QC) samples were thawed, mixed on a vortex mixer, spiked with internal standard (colchicine-d3), and extracted. The extracts were dried under nitrogen, reconstituted, and analyzed using an API 5000 LC-MS/MS equipped with a turbo ion spray source. The multiple reaction monitoring mode was used to monitor the precursor and product ions for the analytes, colchicine, and the internal standard. The analyte and internal standard peak areas were exported to Watson LIMS (Thermo Fisher Scientific Inc., Rochester, New York) to create a calibration curve using weighted ($1/x$) least squares regression fit to a linear model. The concentrations of the standards, QCs, and samples were calculated using Watson LIMS.

The validity of each batch run during subject analysis was determined by evaluating the accuracy of standards and QCs. A batch run was accepted if the standards and QCs passed acceptability criteria. The accuracy and precision of the validation of the bioanalytical method for colchicine was accomplished by analyzing 3 standard curves prepared in human plasma and consisting of 9 concentrations prepared in duplicate in 3 separate batches. QCs were also prepared to assess accuracy, precision, and stability. The standard curve concentrations ranged from 0.2000 to 40.00 ng/mL. The concentrations of the QCs were 0.2000, 0.6000, 3.200, 16.00, and 32.00 ng/mL.

Accuracy was defined as the difference between the mean of a set of results and the "true" value (reported as a percentage; %bias). *Precision* was defined as the %CV of individual replicates from the calculated values. The between-batch accuracy for standards was between 98.57% and 101.92%, while precision was ≤5.60%. The between-batch accuracy of QCs was between 101.17% and 106.22%, while precision was ≤6.38%. The between-batch accuracy for standards was between 98.57% and 101.92%, while precision was ≤5.60%. The between-batch accuracy of QCs was between 101.17% and 106.22%, while precision was ≤6.38%. Within-batch accuracy and precision were assessed by analyzing 6 replicates of QCs at 5 different concentrations (0.2000, 0.6000, 3.200, 16.00, and 32.00 ng/mL). The within-batch accuracy ranged from 96.75% to 109.17%, and precision was ≤5.93%. This method was demonstrated to accurately and precisely quantify all standards and QC samples.

Subjects

Subjects in each study were recruited using identical recruitment criteria. Nonobese (body mass index, 18–32 kg/m^2) adults aged 18 to 45 years of either sex considered healthy on the basis of medical history, physical examination, routine laboratory tests (especially for renal and hepatic function), vital signs, and ECG were eligible for entry into the studies. All subjects had to be nonsmokers (including use of nicotine-containing products) for ≥6 months. Women had to be surgically sterile (hysterectomy or bilateral oophorectomy) or had undergone bilateral tubal ligation ≥6 months before study entry, be sexually inactive for

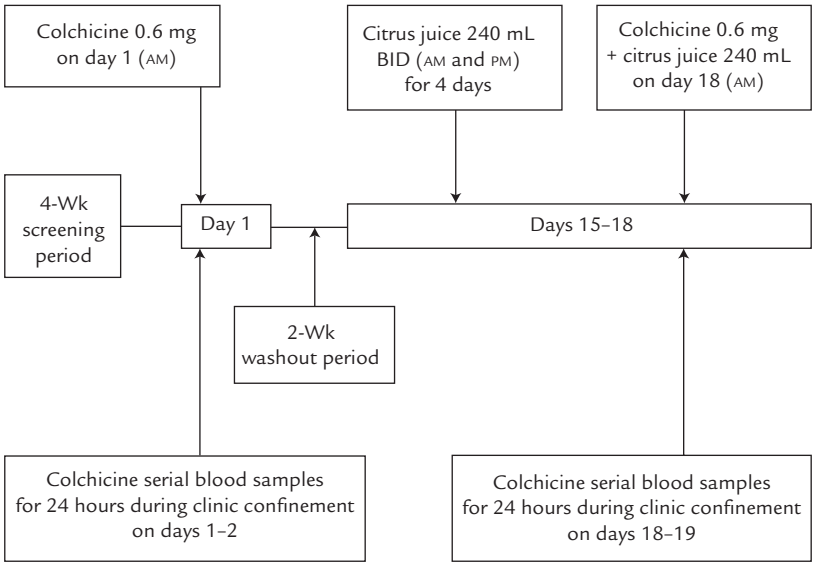

Figure 1. Study design.

≥14 days before the first dose and throughout the study, have sexual activity restricted to a partner who had undergone surgical sterilization ≥6 months prior, or undertake a reliable method of contraception (oral, injectable, topical, or intravaginal hormone contraception for ≥3 months; nonhormonal intrauterine device for ≥3 months and throughout the study; or a barrier method with spermicide for ≥14 days before the first dose and throughout the study). Exclusion criteria included known allergy to colchicine; inability to consume, or food allergy to, grapefruit juice or Seville orange juice (depending on the study); history or presence of significant cardiovascular, pulmonary, hepatic, gallbladder or biliary tract, renal, hematologic, gastrointestinal (GI), endocrine, immunologic, dermatologic, neurologic, or psychiatric disease; use of any drugs or substances known to inhibit CYP enzymes and/or P-gp in the 4 weeks before the first dose and throughout the study; positive test result for HIV or hepatitis B or C at screening; history or evidence of alcoholism or drug abuse in the previous 2 years; active sexually transmitted disease; use of a special diet in the 4 weeks before the first dose; reported difficulty in fasting or consuming standardized meals; hemoglobin <11.5 g/dL; inadequate venous access for repeated venipuncture; blood donation of 50 to 499 mL within 4 weeks and >499 mL within 8 weeks before the first dose; blood donation of >500 mL in 2 weeks, >1500 mL in 6 months, or >2500 mL in 1 year at completion of the study; donation of plasma in the 4 weeks before the first dose; participation in any other clinical trial within 4 weeks before the first dose; and pregnancy or breastfeeding in women.

Study Design

The subjects were recruited and studied at a single US clinical study center (Cetero Research, Fargo, North Dakota), and the study protocols received approval from the institutional review board at PRACS Institute, Ltd (Fargo, North Dakota). All subjects provided written informed consent before participation in the studies, which were conducted in accordance with the US Code of Federal Regulations and International Conference on Harmonisation Guidelines for Good Clinical Practice and adhered to the ethical principles of the Declaration of Helsinki.

The design of each study was identical except for the type of citrus juice administered (grapefruit juice vs Seville orange juice) (**Figure 1**). These Phase I, open-label, nonrandomized, 1-sequence, 2-period pharmacokinetic food–drug interaction studies evaluated the effects of the consumption of 240 mL of citrus juice (grapefruit juice or Seville orange juice in the respective studies) twice daily for 4 consecutive days on the single-dose pharmacokinetic properties of colchicine (0.6-mg tablet) in a fasting state. Following a 4-week

screening period (days −28 to −2), subjects were treated with colchicine 0.6 mg given with 240 mL of water on the morning of day 1 at 7:15 AM. After a washout period ≥14 days, subjects received citrus juice (grapefruit juice or Seville orange juice) 240 mL twice daily on days 15 to 18 at 7:15 AM and 7:15 PM; when not confined, the subjects visited the clinic on a nonconfined basis to receive administration of citrus juices. Study subjects then received a single dose of colchicine 0.6 mg in combination with 240 mL of citrus juice on the morning of day 18. Subjects were admitted to the clinical facility for ~36 hours (~12 hours before dosing and through ~24 hours after dosing) for each period of colchicine dosing alone and in combination with citrus juices (days −1 to 2 and days 17 to 19, respectively). Subjects were dosed in pairs at 1-minute intervals as a single cohort and in the same sequence during each test period. Colchicine doses were administered after completing an overnight fast (10 hours). Compliance was confirmed by oral cavity and hand inspection. No food was permitted until ≥4 hours after dosing. During clinic confinement on days 1 and 18, standardized meals and beverages (free from grapefruit, xanthine- and caffeine-containing products) were provided at 4:25 AM and 10:25 AM, and a standardized snack was provide at 2:25 PM, after colchicine administrations. Meals and snacks were identical during each study period. Water was allowed ad libitum starting 2 hours after colchicine administration. Grapefruit juice was administered as a commercial brand Thirster 100% Grapefruit Juice (Rituals Coffee Co, Columbia, Maryland; lot no.: L 504; expiration date, February 6, 2009), and Seville orange juice was provided as hand-squeezed juice from fresh Seville oranges that was sweetened with 1 tablespoon of aspartame (Equal, The Merisant Company, Chicago, Illinois) to ensure patient compliance. Seville orange juice was obtained by soaking Seville oranges in tepid water for 20 minutes, at which time the rind was removed using a peeler. After removal of the rind, the oranges were then put into a juicer, where the pulp was separated from the rest of the juice. Once juicing was complete, all Seville orange juice was batch frozen to −20°C. The necessary amount of orange juice was removed from the freezer and thawed to room temperature 24 hours prior to administration. Grapefruit juice was refrigerated at 2.8°C to 4.5°C (37°F to 40°F) until dispensed. Neither juice was analyzed for inhibitory components.

Subjects were instructed not to take prescription medications, over-the-counter medications, herbal products, or vitamins or supplements in supratherapeutic doses for 28 days before the first dose of study medication and throughout the study. They were also instructed to abstain from consuming products containing caffeine, xanthine, and alcohol for 48 hours and grapefruit or grapefruit-containing products (apart from scheduled study consumption) for 14 days before the first study dose and throughout the study. They were requested to refrain from engaging in strenuous activities at any time during the confinement periods.

Subjects were free to withdraw from the study at any time for any reason. Furthermore, subjects could be withdrawn by the investigator in the case of unnecessary risk, AEs, or noncompliance.

Medical history, physical examination, vital signs, 12-lead ECG, routine laboratory testing, serum pregnancy screening, and urinary drug screening were performed during the screening period (days −28 to −2). Medical history, physical examination, vital sign measurements, routine laboratory testing, serum pregnancy screening, and urinary drug screening were reassessed at confinement to the clinic on the day before colchicine dosing (days −1 and 17) and at discharge from the clinic at the end of the study (day 22). Urinary drug screening was repeated on day −1. Seated blood pressure and heart rate were measured with the patient in a seated position for ≥5 minutes immediately before colchicine dosing and at 1, 2, and 3 hours postdose on days 1 and 18.

Single-dose colchicine 0.6 mg has been studied in several pharmacokinetic and drug–drug interaction studies[23] completed by the sponsor and, furthermore, total colchicine exposure following a single 0.6-mg dose increased by ~12% to 200% on the basis of C_{max} (maximal observed plasma concentration) and 40% to 240% on the basis of AUC values when given with several known CYP3A4 and P-gp inhibitors.[23] These studies were completed without significant treatment-related AEs, with the most likely AEs being general GI events. In addition, the risk for any serious AEs was considered low, especially given the study entry criteria. Administration of citrus juices (240 mL twice daily for 4 days) has been established in other published drug–food interaction studies to be sufficient for detecting any potential effect on a substrate drug.[23] It

should be noted that a positive control was not used in either study.

Pharmacokinetic Measurements

Methods of pharmacokinetic measurement were identical in each study. Blood (6-mL aliquots) was taken by direct venipuncture before dosing (time 0) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose on days 1 and 18 (during confinement) and at 36, 48, 72, and 96 hours postdose (returning to the clinic on a nonconfined basis). All blood samples (192 mL) were collected into K_2-EDTA tubes, kept on ice, and then centrifuged at ~2500*g* at 4°C for 15 minutes. Plasma samples were stored at −20°C or colder and transferred to the bioanalytical laboratory (Cetero Research), where they were assayed, by personnel masked as to the study details or sequence, for colchicine using a validated method of LC-MS/MS.

Pharmacokinetic properties were determined using WinNonlin version 5.0.1 (Pharsight, Mountain View, California) using standard noncompartmental methods to determine the following pharmacokinetic parameters: C_{max}, T_{max}, AUC_{0-t} (calculated by the linear trapezoidal method), $AUC_{0-\infty}$ (calculated as $AUC_{0-t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant), k_{el} (apparent first-order terminal elimination rate calculated from a semi-log plot of the plasma concentration versus time curve calculated by linear least squares regression analysis using the maximal number of points in the terminal log-linear phase [eg, ≥3 nonzero plasma concentrations]), $t_{½}$ (apparent first-order terminal elimination half-life, calculated as $0.693/k_{el}$), CL/F (apparent total body clearance, calculated as the dose/$AUC_{0-\infty}$), and V_{area}/F (apparent total volume of distribution, calculated as the dose/[$AUC_{0-\infty} \times k_{el}$]). Samples with significant deviation from protocol-schedule times were not included in the analysis.

Statistical Analysis

Statistical analysis was identical in each study. No formal sample size determination was performed. However, it was estimated that 24 subjects would be adequate based on sample sizes used in other published drug–food interaction studies with citrus juices.[23] It has also been reported to be sufficient for detecting significant interactions with colchicine in drug–drug interaction studies undertaken by the sponsor.[23]

Descriptive statistics were used to summarize the pharmacokinetic data. ANOVA were performed using the SAS General Linear Model (GLM) procedure on the log (ln)-transformed geometric mean colchicine AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} comparing administration of colchicine with and without citrus juice. The ANOVA model included study drug as a fixed effect and subject as a random effect. Each ANOVA included calculation of least squares means (LSM), the difference between study drug LSM and the SE associated with this difference. Ninety percent CIs for the ratios were derived by exponentiation of the CI obtained for the difference between study drug LSM resulting from the analyses on the ln-transformed geometric mean AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} values. The Wilcoxon signed rank test statistic was used to analyze T_{max}, with a P value <0.05 considered as significant.

RESULTS

In study 1 (grapefruit juice), all subjects received the first dose of study medication on September 13, 2008, and the last pharmacokinetic blood sample was collected on October 4, 2008. In study 2 (Seville orange juice), all subjects received the first dose of study medication on February 19, 2009, and the last pharmacokinetic blood sample was collected on March 9, 2009.

A total of 22 subjects initiated study 1 (grapefruit juice) and 24 subjects initiated study 2 (Seville orange juice). Despite the protocol requiring 24 participants in each study, the lower number recruited in study 1 was not considered to have significantly affected the determination of the effect of consecutive grapefruit juice administrations on single-dose colchicine concentrations. Subjects enrolled in either study and who took ≥1 dose of study drug were included in the overall tolerability evaluations for the relevant study.

One subject was discontinued from each study due to missing a morning consumption of citrus juice, which was considered a major protocol violation, in the second period of the study. Therefore, 21 subjects in study 1 (grapefruit juice) and 23 subjects in study 2 (Seville orange juice) had paired pharmacokinetic data analyzed in the statistical ANOVA. There were no other major protocol deviations. Of the number of minor protocol deviations that occurred during the conduct of both studies, none were considered to

Table I. Baseline demographic characteristics of the subjects in the studies of the effects of grapefruit and Seville orange juices on the pharmacokinetic properties of colchicine.

Characteristic	Grapefruit Juice (Study 1) (n = 22)	Seville Orange Juice (Study 2) (n = 24)
Age, mean (range), y	26.9 (21–45)	25.8 (18–40)
Sex, no. (%)		
Male	16 (72.7)	9 (37.5)
Female	6 (27.3)	15 (62.5)
Ethnicity, no. (%)		
White	20 (90.9)	24 (100)
Black	2 (9.1)	0
Height, mean (range), in.	70.3 (61.3–75.5)	67.9 (61.9–75.2)
Weight, mean (range), lb	180.3 (128–235.5)	161.8 (116.5–240.0)
Body mass index, mean (range), lb/in^2	25.5 (20.6–31.3)	24.5 (19.2–30.6)

have had an effect on the interpretation of the study results.

The demographic characteristics of each protocol population in each study are summarized in Table I. In study 1 (grapefruit juice), the majority of the subjects were male (72.7%) and white (90.9%). In study 2 (Seville orange juice), the majority of the subjects were female (62.5%), and all were white.

Pharmacokinetic Properties of Colchicine Administered With and Without Grapefruit Juice (Study 1)

Plasma concentration versus time curves for colchicine appeared remarkably similar after administration with and without grapefruit juice (Figure 2A). Nontransformed, arithmetic pharmacokinetic parameters comparing colchicine administered with and without grapefruit juice are summarized in Table II. There were scant apparent differences in the pharmacokinetic properties of colchicine administered with and without grapefruit juice. Consumption of grapefruit juice slightly decreased the arithmetic mean colchicine C_{max} (1.97 vs 2.17 ng/mL, respectively), AUC_{0-t} (8.82 vs 9.33 ng · h/mL), $AUC_{0-\infty}$ (10.85 vs 11.08 ng · h/mL), and k_{el} (0.153 vs 0.171 h^{-1}) and increased V_{area}/F (433.1 vs 363.9 L). Median colchicine T_{max} was significantly increased with grapefruit juice consumption (1.5 vs 1.0 hour; $P = 0.0156$).

The following statistical analyses were undertaken to determine whether a clinically significant food–drug interaction was present in accordance with FDA guidelines.[24] The ln-transformed geometric mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values for colchicine administered with and without grapefruit juice are summarized in Table III. The associated 90% CI of the ratios of the ln-transformed geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the FDA-accepted interval defining "no interaction" (80%–125%), suggesting that no food–drug interaction is present when colchicine and grapefruit juice are coadministered.

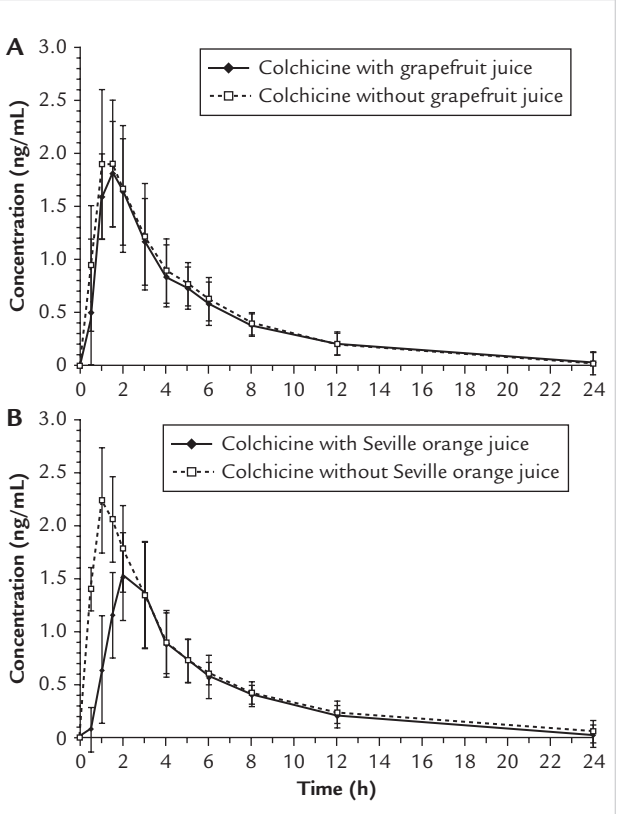

Figure 2. Mean plasma colchicine concentrations after the administration of a single oral dose of colchicine 0.6 mg with (A) grapefruit juice (n = 21) and (B) Seville orange juice (n = 23) in healthy subjects.

Table II. Pharmacokinetic properties of colchicine after the administration of a single oral dose of colchicine 0.6 mg with and without grapefruit juice in healthy subjects (n = 21).

	Colchicine With Grapefruit Juice (Test)		Colchicine Without Grapefruit Juice (Reference)	
Property	Mean (SD)	%CV	Mean (SD)	%CV
AUC_{0-t}, ng · h/mL	8.82 (3.00)	34.04	9.33 (3.37)	36.10
$AUC_{0-\infty}$, ng · h/mL	10.85 (4.14)	38.14	11.08 (3.95)	35.64
C_{max}, ng/mL	1.97 (0.40)	20.23	2.17 (0.65)	30.05
T_{max}, h*	1.5 (1.0–3.0)	–	1.0 (1.0–2.0)	
k_{el}, h^{-1}	0.153 (0.05)	34.78	0.171 (0.05)	29.22
$t_{½}$, h	5.58 (3.51)	62.79†	4.64 (2.52)	54.29†
V_{area}/F, L	433.1 (117.2)	27.1	363.9 (97.34)	26.75
CL/F, L/h	62.18 (21.42)	34.45	60.25 (21.26)	35.29
Weight-adjusted CL/F, L/h/kg	0.76 (0.29)	37.88	0.74 (0.30)	40.60

CL/F = apparent total body clearance; k_{el} = apparent first-order terminal elimination rate constant; V_{area}/F = apparent total volume of distribution.
*Median (range).
†An underestimation because the majority of plasma concentrations were not quantifiable by 24 hours postdose.

Pharmacokinetic Properties of Colchicine Administered With and Without Seville Orange Juice (Study 2)

Plasma concentration versus time curves for colchicine after administration with and without Seville orange juice showed marked differences (**Figure 2B**). Nontransformed, arithmetic pharmacokinetic properties comparing colchicine administered with and without Seville orange juice are summarized in **Table IV**. Both C_{max} and AUC appeared to have decreased during coadministration with Seville orange juice. Consumption of Seville orange juice decreased arithmetic mean colchicine C_{max} (1.67 vs 2.33 ng/mL, respectively), AUC_{0-t} (7.63 vs 10.26 ng · h/mL), $AUC_{0-\infty}$ (9.15 vs 12.07 ng · h/mL), and $t_{½}$ (4.91 vs 5.54 hours) and increased CL/F (70.14 vs 57.03 L/h) and V_{area}/F (472.2 vs 413.7 L). Median colchicine T_{max} was significantly increased by Seville orange juice consumption (2.0 vs 1.0 hour; $P < 0.0001$). It should be noted that the $t_{½}$ and CL/F were poorly estimated because the terminal elimination slope could not be estimated.

The ln-transformed geometric mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values for colchicine administered with and without Seville orange juice are summarized in **Table V**. Peak exposure (C_{max}) and extent of exposure

Table III. Geometric mean ln-transformed pharmacokinetic properties of colchicine after the administration of a single oral dose of colchicine 0.6 mg with and without grapefruit juice in healthy subjects (n = 21).

Property	Colchicine With Grapefruit Juice (Test)	Colchicine Without Grapefruit Juice (Reference)	% Ratio (Test/Reference)	90% CI
AUC_{0-t}, ng · h/mL	8.35	8.81	94.85	86.47–104.04
$AUC_{0-\infty}$, ng · h/mL	10.21	10.50	97.26	88.08–107.40
C_{max}, ng/mL	1.93	2.07	93.25	83.07–104.67

Table IV. Pharmacokinetic properties of colchicine after the administration of a single oral dose of colchicine 0.6 mg with and without Seville orange juice in healthy subjects (n = 23).

	Colchicine With Seville Orange Juice (Test)		Colchicine Without Seville Orange Juice (Reference)	
Property	Mean (SD)	%CV	Mean (SD)	%CV
AUC_{0-t}, ng · h/mL	7.63 (2.68)	35.08	10.26 (4.31)	41.98
$AUC_{0-\infty}$, ng · h/mL	9.15 (2.74)	29.99	12.07 (4.66)	38.59
C_{max}, ng/mL	1.67 (0.42)	25.38	2.33 (0.98)	42.09
T_{max}, h*	2.0 (1.5–3.0)	–	1.0 (0.5–2.0)	–
k_{el}, h^{-1}	0.155 (0.04)	26.55	0.146 (0.05)	37.32
$t_{½}$, h	4.91 (1.87)	38.09	5.54 (2.39)	43.18
V_{area}/F, L	472.2 (120.4)	25.49	413.7 (137.1)	33.13
CL/F, L/h	70.14 (17.07)	24.34	57.03 (22.01)	38.60
Weight-adjusted CL/F, L/h/kg	0.99 (0.32)	32.03	0.80 (0.30)	37.34

CL/F = apparent total body clearance; k_{el} = apparent first-order terminal elimination rate constant; V_{area}/F = apparent total volume of distribution.
*Median (range).

(AUC values) for colchicine were decreased by ~25% and ~20%, respectively, during coadministration with Seville orange juice. The 90% CI ratios of the ln-transformed geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were outside of the FDA-accepted interval for "no interaction" (80%–125%), suggesting that a clinically significant food–drug interaction was present when colchicine and Seville orange juice were coadministered.

Tolerability

All subjects were monitored for AEs throughout the confinement portion of the study and queried during the nonconfinement visits. Blood pressure (sitting for ≥5 minutes) and pulse were measured prior to dosing (time 0) and at 1, 2, and 3 hours postdose on days 1 and 18, as well as at screening, each check-in, and study exit (day 19 or early termination). All subjects underwent clinical laboratory testing, including hematology, biochemistry, urinalysis, and in women, pregnancy testing at screening, baseline, period 2 check-in (day 17), and prior to discharge from the study (urinalysis was not done at discharge). A full physical examination was performed at screening, with targeted physical examinations conducted at baseline, day 18, and study discharge if needed in response to AEs or changes in medical history.

Treatment-emergent AEs, defined as those with onset coinciding with, or subsequent to, the administration of the drug, are summarized in **Table VI**.

Table V. Geometric mean ln-transformed pharmacokinetic properties of colchicine after the administration of a single oral dose of colchicine 0.6 mg with and without Seville orange juice in healthy subjects (n = 23).

Property	Colchicine With Seville Orange Juice (Test)	Colchicine Without Seville Orange Juice (Reference)	% Ratio (Test/Reference)	90% CI
AUC_{0-t}, ng · h/mL	7.25	9.42	76.99	65.14–90.99
$AUC_{0-\infty}$, ng · h/mL	8.97	11.34	79.07	69.15–90.40
C_{max}, ng/mL	1.62	2.12	76.24	65.83–88.29

Table VI. Treatment-emergent adverse events following oral administration of a single dose of colchicine 0.6 mg alone and in combination with citrus juice (grapefruit or Seville orange) to healthy subjects.

	No. of Subjects Experiencing AEs (%)			
	Study 1		Study 2	
AE	Colchicine 0.6 mg Alone (N = 22)	Colchicine 0.6 mg + Grapefruit Juice (N = 21)	Colchicine 0.6 mg Alone (N = 24)	Colchicine 0.6 mg + Seville Orange Juice (N = 23)
Any AE	1 (4.5)	2 (9.5)	5 (20.8)	1 (4.3)
AE by preferred term*				
Headache	1 (4.5)	0	2 (8.3)	1 (4.3)
Cough	0	1 (4.8)	2 (8.3)	0
Dyspepsia	0	0	1 (4.2)	0
Diarrhea	0	1 (4.8)	1 (4.2)	0
Chest congestion	0	1 (4.8)	0	0
Pharyngolaryngeal pain	0	1 (4.8)	1 (4.3)	1 (4.3)
Pyrexia	0	0	1 (4.2)	0
Pain	0	0	1 (4.2)	0

MedDRA = Medical Dictionary for Regulatory Affairs.
*According to MedDRA Version 10.1.

There were no reports of serious AEs, discontinuations because of AEs, or deaths. All AEs were mild or moderate in intensity. There were no clear between-treatment differences in either study. In study 1, treatment-emergent AEs were reported in 2 and 1 patients who received colchicine with and without grapefruit juice, respectively. In study 2, a higher percentage of subjects receiving colchicine without Seville orange juice experienced treatment-emergent AEs compared with colchicine administered with Seville orange juice (20.8% vs 4.3%). However, 2 of the 5 subjects receiving colchicine without Seville orange juice had multiple AEs related to upper respiratory infection (cough/diarrhea/headache and pharyngolaryngeal pain/headache, respectively) and were considered not related to treatment. There was a report of mild dyspepsia and diarrhea in 1 subject (4.2%). There were no reports of treatment-related GI effects. No consistent changes were reported during the study with respect to laboratory values, vital sign measurements, or physical findings. Treatment-emergent abnormalities were unremarkable, and none of the values were outside of normal limits, clinically significant, or directly attributable to the study medication.

DISCUSSION

Consumption of grapefruit juice (240 mL twice daily for 4 consecutive days) had no statistically or clinically significant effects on the pharmacokinetic properties of colchicine following the oral administration of a single 0.6-mg dose in healthy subjects in a fasted state except for a marginal but statistically significant increase in median T_{max}, from 1.0 to 1.5 hours ($P = 0.0156$). Paradoxically, consumption of Seville orange juice (240 mL twice daily for 4 consecutive days) decreased colchicine C_{max} and overall total colchicine exposure (AUC values) by ~25% and ~20%, respectively, on the basis of ln-transformed geometric mean values. Median colchicine T_{max} was also significantly increased, from 1.0 to 2.0 hours ($P < 0.0001$), delayed by ~1 hour during Seville orange juice consumption. The clinical significance of this finding is unknown. The findings of these 2 studies were unexpected, because previous studies and case reports in the literature indicated that both citrus juices would be expected to increase systemic colchicine exposures.

Mechanistically, it has been well established in the published literature that grapefruit juice is an inhibitor of the intestinal CYP3A4 and can lead to clinically

significant interaction with certain drugs that are CYP3A4 substrates (eg, felodipine, amiodarone, atorvastatin), resulting in increased systemic exposure (for recent reviews, see Seden et al,[4] Won et al,[5] and Hanley et al[6]). This is believed to be the primary mechanism by which grapefruit juice can increase systemic drug exposure. Bergamottin and 6′,7′-dihydroxybergamottin are believed to be the main compounds effecting CYP3A4 inhibition induced by grapefruit juice and similarly by Seville orange juice.[7] However, it has also been suggested that inhibition of intestinal P-gp may also be involved in grapefruit juice–drug interactions, resulting in increased systemic exposure. Indeed, grapefruit juice has been reported to inhibit P-gp–mediated efflux transport of colchicine in vitro.[25] More recently, these investigators have reported that GI absorption of colchicine is decreased throughout the small intestine by the combined effects of P-gp and multidrug resistance–associated protein 2 transepithelial efflux dominating the GI permeability process.[26] The clinical relevance of this is not known because these findings have not been reproduced in human subjects or in patients with known P-gp substrates.[4]

The paradoxical decrease in colchicine exposure during coadministration with Seville orange juice was unexpected and raises a number of questions. Other mechanisms have been implicated in interactions of citrus juice (grapefruit juice or sweet orange juice) with medications, including inhibition of uptake transporters such as organic anion-transporting polypeptides (OATPs) (for reviews, see Bailey,[27] Seden et al,[4] Won et al,[5] and Hanley et al[6]). Grapefruit juice and sweet orange juice have been reported to inhibit OATP-mediated drug transport in vitro.[28,29] Naringin has been reported to be one of the components of grapefruit juice involved in OATP inhibition.[30] Inhibition of OATP-mediated enterocyte drug uptake (ie, active GI absorption) by grapefruit juice and/or sweet orange juice has been reported to significantly decrease peak exposures and extent of systemic exposures of certain drugs that undergo active OATP-mediated GI absorption (eg, fexofenadine,[28] celiprolol,[31] talinolol,[32] atenolol,[33] aliskiren,[34] ciprofloxacin,[35] and etoposide[36]).

It is unknown whether colchicine undergoes OATP-mediated GI absorption. Furthermore, grapefruit juice had no effect on the pharmacokinetic properties of colchicine in the present study. It might be hypothesized that some other, unknown component of Seville orange juice not present in grapefruit juice might be responsible for inhibition of colchicine absorption via the OATP-mediated pathway. There are few studies on the interaction of Seville orange juice with agents apart from felodipine,[7] where it behaves similarly to grapefruit juice. In addition, there have been few studies on the composition of Seville orange juice, although the furocoumarin bergapten has been identified as a component of Seville orange juice, which is not a constituent in grapefruit juice.[7] These investigators suggested that Seville orange juice appears to selectively inhibit intestinal CYP3A4 (and not P-gp), whereas grapefruit juice inhibits both intestinal CYP3A4 and P-gp.[7] Both C_{max} and AUC were significantly decreased during coadministration of Seville orange juice in the present study (ln-transformed geometric mean C_{max} and AUC values were reduced by ~25% and ~20%, respectively). Other PK parameters affected during concurrent administration of colchicine and Seville orange juice include T_{max}, which was increased by 1 hour (median).

Despite no findings of clinically significant interaction between grapefruit juice consumption and the single-dose pharmacokinetic properties of colchicine in this study, the FDA has maintained that grapefruit juice is a moderate CYP3A4 inhibitor in the drug labeling for approved colchicine, which necessitates adjusted, lower doses of colchicine because of a potential for increased systemic colchicine exposure and AEs. Specific recommendations for dosing adjustments when using colchicine together with moderate CYP3A4 inhibitors (eg, grapefruit juice) in the prophylaxis or treatment of patients with gout flares are available in the full prescribing information. Alternatively, normal doses of colchicine can be used, but grapefruit-containing products should be avoided.[37]

Review of the literature reveals few data regarding the potential for interaction between colchicine and grapefruit juice. A single case report of near-fatal acute colchicine toxicity with concurrent consumption of grapefruit juice was reported in an 8-year-old girl with familial Mediterranean fever.[38] This patient had been prescribed colchicine 2 mg/d for 10 months and, during the 2 months preceding hospital admission, was ingesting 1000 mL/d of grapefruit juice. She developed fever, recurrent vomiting, severe abdominal pain, and a sore throat. She was hospitalized 2 days later for an acute attack of familial Mediterranean fever. By day 2, the patient developed circulatory shock and pancytopenia, requiring intubation, fluid support, inotropic agents, fresh frozen plasma, vitamin K, and granulocyte colony-stimulating

factor. The patient's clinical condition improved and stabilized during the following days. Delayed pathologies present in the second week of hospitalization included practically total alopecia, atonic falls, weakness, and an elevated white blood cell count, with no signs of infection. These symptoms resolved by the patient's discharge from the hospital on day 24. Based on a thorough search of the published literature, there have been no other reports concerning the potential interaction between grapefruit juice and colchicine to the authors' knowledge.

CONCLUSIONS

In consideration of the fact that a positive control was not used in either study, based on mechanism of action as a moderate CYP3A4 inhibitor, grapefruit juice unexpectedly did not affect the pharmacokinetic properties of colchicine. Paradoxically, Seville orange juice reduced C_{max} and AUC and increased T_{max}. Colchicine administered in combination with either juice was well tolerated.

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CONFLICTS OF INTEREST

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