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