Repeated Ingestion of Grapefruit Juice Does Not Alter Clozapine's Steady-State Plasma Levels, Effectiveness, and Tolerability

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Background: Grapefruit juice can inhibit the gastrointestinal activity of cytochrome P450 (CYP) 3A4, while its effect on CYP1A2 remains controversial. Several grapefruit juice bioflavonoids also modulate the activity of the drug transporter P-glycoprotein in the gut and in the blood-brain barrier. Both CYP1A2 and CYP3A4 are involved in clozapine metabolism. This study investigated the effects of repeated ingestion of grapefruit juice on multiple-dose pharmacokinetics and pharmacodynamics of clozapine in schizophrenic patients.

Method: Clozapine therapy was initiated for fifteen treatment-resistant schizophrenic inpatients (DSM-IV criteria). The doses were individually titrated from day –35 to day –15 and then kept unchanged from day –14 to day 49. Regular-strength grapefruit juice (250 mL) was coadministered b.i.d. with each clozapine dose from day 15 to day 28. Plasma levels of clozapine and its main metabolites (norclozapine and clozapine *N*-oxide) were obtained, and clinical efficacy and safety assessments were completed prior to juice administration (days 0, 7, and 14), during the coadministration (days 17, 21, and 28), and after cessation of the juice (days 35, 42, and 49).

Results: After reaching steady states, plasma concentrations of clozapine and its metabolites and Positive and Negative Syndrome Scale scores were not significantly altered by the effect of grapefruit juice ingestion. The Clinical Global Impressions scale scores, Calgary Depression Scale scores, and side effect profiles (by the Extrapyramidal Symptom Rating Scale, the UKU Side Effect Rating Scale, and thorough examinations including electrocardiography and electroencephalography) also remained constant during the study.

Conclusion: Consumption of regular-strength grapefruit juice, 250 mL b.i.d., for 14 days did not significantly impact clozapine metabolism, clinical efficacy, or tolerability. One reason is that enzymes other than CYP3A4 also mediate clozapine disposition. Also, grapefruit juice inhibits CYP3A4 in the gut, but not in the liver. The preliminary results also suggest that clozapine is unlikely to be a P-glycoprotein substrate. Further rigorous studies are necessary to reconfirm these findings.

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An explosion of information about drug and diet interactions has greatly complicated the use of many drugs, including psychotropic agents.[1] Grapefruit juice contains bioflavonoids or other compounds that inhibit the activity of cytochrome P450 (CYP) 3A4 in the gut wall.[2] Whether grapefruit juice also influences CYP1A2 remains controversial.[1,3,4] Coadministration with grapefruit juice increases markedly (up to 3- to 12-fold) blood concentrations of numerous drugs,[1,5,6] including midazolam,[6] triazolam,[6] diazepam,[7] buspirone,[8] sertraline,[9] some calcium channel blockers,[6,10] cyclosporine,[6] terfenadine,[2,6] and lovastatin.[11]

Grapefruit juice bioflavonoids also modulate the activity of the drug transport system P-glycoprotein in the gut[12] and in the blood-brain barrier.[13] P-glycoprotein reduces drug absorption through the gastrointestinal tract as it promotes drug movement from intracellular contents back into the intestinal lumen.[14,15] Similarly, in the blood-brain barrier, P-glycoprotein restricts permeability of the vascular epithelium by pumping drugs back into blood and thus decreasing the brain penetration and pharmacologic activity of many drugs.[16] Grapefruit juice could activate P-glycoprotein and decrease amounts of P-glycoprotein substrates in the body.[12] However, recent research indicates that the grapefruit juice effects on P-glycoprotein might be dose-dependent: low doses could stimulate P-glycoprotein and high doses could inhibit it.[13] Since grapefruit juice activity occurs not only in the gut but also in the brain, stud-

ies regarding grapefruit juice–drug interactions should include pharmacodynamic measures. Peripheral pharmacokinetics may only partially contribute to the interactions.

Clozapine, the prototypical atypical antipsychotic agent, is the substrate of CYP1A2, CYP3A4, and other enzymes.[17,18] Fluvoxamine, an inhibitor for CYP1A2, CYP3A4, and other isoforms, reduces the clozapine dosage (and thus the cost) needed in refractory schizophrenic patients.[19] Whether grapefruit also has the same potential remains unknown. P-glycoprotein is a very weak transporter of clozapine in vitro and in mice receiving medications via intravenous routes.[16] However, transportation of clozapine by P-glycoprotein is worthy of examination in human beings, because clozapine's oral bioavailability in patients is quite low at 0.27.[17] It is thus warranted to study the effects of grapefruit on pharmacokinetics and pharmacodynamics of clozapine.

Steady-state plasma clozapine levels were reported to be unaffected by short-term (2-day) consumption of 500 mL/day of grapefruit juice in 9 patients.[20] In another study with fewer subjects (N = 5, none of whom participated in the current study), 7-day administration of 500 mL/day of regular strength grapefruit juice had a trend (without statistical significance) to lower the mean area under the plasma concentration time curve of single-dose clozapine (H.-Y.L., unpublished data, Sept. 2000). Pharmacodynamic data were lacking in these studies. Furthermore, repeated consumption of grapefruit juice results in a cumulative increase in the P-glycoprotein activity.[6,10,21] Also, the pharmacokinetic effects of grapefruit juice may be highly variable among individuals.[2,11]

Longer duration of juice ingestion, a larger number of study subjects, and inclusion of pharmacodynamic assessments are needed to substantiate previous findings on clozapine's interaction with grapefruit juice. The present study investigated the effects of 14-day administration of regular strength grapefruit juice, 500 mL/day, on multiple-dose pharmacokinetics and pharmacodynamics of clozapine in schizophrenic patients.

METHOD

Subjects

This was a prospective, open-label study conducted in a research ward. The facility's institutional review board approved the project. Fifteen Chinese inpatients (9 women and 6 men, mean ± SD age = 35.3 ± 9.1 years; mean body weight = 64.0 ± 13.7 kg [142.2 ± 30.4 lb], all nonsmokers) participated in the study. They gave informed consent and were fully competent to do so. They met DSM-IV diagnostic criteria for schizophrenia and were treatment-resistant to at least 2 classes of antipsychotics. They had not been previously treated with clozapine; had not received depot antipsychotics for at least 6 months prior to the study; had not consumed beverages containing caffeine, alcohol, or grapefruit juice for at least 1 month; and had not taken any known compounds that may affect the activities of CYP isoforms[18,22] or P-glycoprotein[14,15] for a minimum of 2 weeks. They were physically healthy and received complete physical examinations and urinalysis, blood chemistry and hematologic, electrocardiography (ECG), and electroencephalography (EEG) assessment before clozapine treatment. Results of examinations were within normal limits.

Study Design

Before the beginning of the study, all previous medications were discontinued. Clozapine was then started, and the doses were individually titrated from day –35 to day –15 and kept unchanged, with a mean dose of 248.3 ± 115.9 mg/day (range, 75–500 mg/day) from day –14 to day 49. Regular-strength grapefruit juice (Ocean Spray Cranberries, Inc., Lakeville-Middleboro, Mass.), 250 mL, was coadministered b.i.d. with each clozapine dose from day 15 to day 28. Trough plasma levels of clozapine and its main metabolites (norclozapine and clozapine *N*-oxide) as well as clinical effectiveness and tolerability were assessed before ingestion of grapefruit juice (on the morning of days 0, 7, and 14), during the coadministration (days 17, 21, and 28), and after cessation of the juice (days 35, 42, and 49).

Clinical Assessment

Efficacy and side effect assessments were conducted on each visit day. The main efficacy instrument was the Positive and Negative Syndrome Scale (PANSS).[23] Other measures included the Clinical Global Impressions scale (CGI)[24] and the Calgary Depression Scale (CDS).[25] The CDS is a valid and reliable instrument for assessing mood in schizophrenic patients.[25]

Drug safety was evaluated by means of thorough physical and neurologic examinations, the Extrapyramidal Symptom Rating Scale (ESRS),[26] and the UKU Side Effect Rating Scale.[27] The ESRS was designed to evaluate 3 types of extrapyramidal symptoms: parkinsonism, dystonia, and dyskinesia. Other side effect profiles were determined by the UKU scale. An experienced research psychiatrist (H.-Y.L.) conducted all psychopathology and side effect ratings. Vital signs were monitored at least once per day, and physical, neurologic, and hematology examinations were performed at least once per week. Blood chemistry tests, EEG, and ECG were repeated on day 14 (before the coadministration period) and day 28 (the endpoint of the coadministration).

Laboratory Assessment

Plasma concentrations of clozapine and its 2 main metabolites, norclozapine and clozapine *N*-oxide, were assayed by high-performance liquid chromatography with ultraviolet detection.[28] The intra-assay and interassay coefficients

Table 1. Plasma Levels of Clozapine and Its Metabolites Before, During, and After Coadministration of Regular Strength Grapefruit Juice, 250 mL b.i.d., in 15 Schizophrenic Inpatients Receiving Clozapine

	Clozapine (ng/mL)		Norclozapine (ng/mL)		Clozapine *N*-Oxide (ng/mL)	
Timepoint	Mean	SD	Mean	SD	Mean	SD
Before grapefruit juice						
Day 0	371.3[a]	197.8	182.5[a]	99.1	51.1	25.3
Day 7	390.1[b]	202.6	196.6[b]	98.9	57.4	28.3
Day 14	400.9[b]	210.7	200.7[b]	112.9	55.4	24.6
With grapefruit juice						
Day 17	459.3	255.9	210.6	119.1	60.8	31.2
Day 21	453.1	247.5	218.9	126.2	56.0	26.6
Day 28	422.1	204.6	212.0	102.3	54.0	26.6
After cessation of grapefruit juice						
Day 35	424.9	188.8	212.8	100.9	52.6	27.4
Day 42	429.3	215.9	208.2	109.3	56.0	23.7
Day 49	449.5	226.1	220.7	103.3	58.7	24.7

[a] $p < .005$ versus endpoint (day 49).
[b] $p < .05$ versus endpoint (day 49) after controlling for other prognostic variables (multiple linear regression analysis with the generalized estimating equation method).

of variation were 8.0% to 14.7% at 50 ng/mL for clozapine and its metabolites. The lower limits of detection were 1 ng/mL for clozapine and 2 ng/mL for norclozapine and clozapine *N*-oxide. All samples were assayed in duplicate.

Statistical Analysis

The multiple linear regression model was used to evaluate the possible effects of the prognostic variables on plasma concentrations of clozapine and metabolites and the scores of various rating scales. The prognostic variables included clozapine dose, gender, age, body weight, and study days. Due to the repeated measurements of each subject, the generalized estimating equation (GEE) method[29] was utilized to take into account the within-subject dependence. An α level of .05 for type I errors was employed. The PROC GENMOD procedure from the SAS/STAT V6.12 system[30] was used to analyze the data.

RESULTS

Plasma Drug Levels

By the GEE method's multiple linear regression model, clozapine dose, gender, and study day were found to alter plasma levels of clozapine and its metabolites. After controlling for other prognostic variables, each 1-mg dose increment could raise the mean ± SEM plasma clozapine concentration by 1.8 ± 0.3 ng/mL, the plasma norclozapine concentration by 0.7 ± 0.2 ng/mL, and the plasma clozapine *N*-oxide concentration by 0.2 ± 0.0 ng/mL ($p < .0001$ for each). Female patients had higher plasma clozapine levels by 192.6 ± 67.1 ng/mL ($p < .005$). The gender influences on the metabolites were not significant in this small population. Each 1-year increase in age also elevated plasma norclozapine by 2.5 ± 1.0 ng/mL ($p < .05$). These gender and age effects are similar to those found in earlier studies.[31,32]

Table 1 shows plasma levels of clozapine and its metabolites from day 0 to day 49. Plasma levels of clozapine and norclozapine appeared to rise gradually from day 0 to day 14 (the period prior to grapefruit juice consumption) and then reach a plateau from day 17 to day 49 (the periods during and after juice ingestion). After controlling for other prognostic variables by the GEE method, the mean plasma level of clozapine and norclozapine on days 0, 7, and 14 was lower than that on day 49. However, the mean plasma level of both compounds at each of the visits following day 14 was comparable with that on day 49. Previous investigators[33] have demonstrated that the enzyme inhibition effects of grapefruit juice, even after repeated ingestion, are reversible soon after discontinuation of the juice. Therefore, in the present study, a better explanation for the gradually increasing clozapine and norclozapine levels from day 0 to day 17 might be that the plasma levels were approaching the steady states. The effect of grapefruit juice per se is a less likely explanation for the increasing levels. The change in plasma clozapine *N*-oxide levels did not achieve statistical significance.

Clinical Effectiveness

Mean ± SD PANSS total scores are shown in Table 2. After controlling for other variables, the mean scores on days 0, 7, 14, and 17 (but none of other days) were significantly higher than that on day 49 ($p < .01$ for each). After steady states of plasma drug levels were achieved, PANSS scores soon became stable and were not changed after cessation of grapefruit juice. All mean CGI scores were similar across the assessment days. Few patients had a CDS score > 0 at the visits (see Table 2).

Tolerability

Addition of grapefruit juice to clozapine was well tolerated and did not produce newly observed, clinically rel-

Table 2. Effectiveness and Tolerability of Clozapine Prior to, During, and After Coadministration of Grapefruit Juice[a]

	Before Grapefruit Juice			With Grapefruit Juice			After Grapefruit Juice		
Measure	Day 0	Day 7	Day 14	Day 17	Day 21	Day 28	Day 35	Day 42	Day 49
Effectiveness ratings									
PANSS, mean (SD)	77.0 (9.6)	71.7 (8.7)	69.5 (10.4)	71.8 (11.4)	67.5 (12.3)	65.3 (12.5)	64.0 (12.3)	64.7 (13.4)	65.3 (15.0)
CGI, mean (SD)	4.7 (0.7)	4.5 (0.8)	4.4 (0.8)	4.4 (0.8)	4.3 (0.7)	4.3 (0.7)	4.2 (0.7)	4.2 (0.7)	4.3 (0.8)
CDS score > 0, N	2	1	1	2	1	2	1	0	0
Tolerability ratings									
ESRS									
Parkinsonism, mean (SD)	2.9 (6.7)	2.6 (5.2)	2.8 (4.9)	3.0 (4.8)	2.9 (5.3)	2.8 (5.1)	3.1 (6.2)	3.1 (6.2)	3.0 (6.3)
Dyskinesia score > 0, N	2	2	2	2	2	2	1	1	1
UKU									
Tachycardia, N	5	4	4	4	4	5	5	3	3
Salivation, N	3	3	1	1	1	0	0	0	0
Weight gain, N	3	2	2	2	2	2	2	2	1
Constipation, N	2	3	3	3	2	1	0	0	0
Fatigability, N	2	3	2	2	2	2	1	1	1
Sedation, N	2	2	1	2	2	2	3	2	1

[a]Abbreviations: CDS = Calgary Depression Scale, CGI = Clinical Global Impressions scale, ESRS = Extrapyramidal Symptom Rating Scale, PANSS = Positive and Negative Syndrome Scale, UKU = UKU Side Effect Rating Scale.

evant side effects. Significant adverse reactions were also not evident after withdrawal of the juice (see Table 2). Regarding the ESRS, the mean parkinsonism scores were quite low and constant at the visits (p = NS vs. endpoint for each). Very few patients had a dyskinesia score > 0. No patients experienced dystonia. Concerning the UKU scale, the most common event was tachycardia. Other, less common events included salivation, weight gain, constipation, fatigability, and sedation. These events were all mild or moderate.

Slowing on EEG was found in 7 patients (47%) before juice consumption (on day 14) and in 6 patients (40%) at the endpoint of coadministration (on day 28). Spikes on EEG (without clinical seizures) developed in 1 patient on day 14 but subsided on day 28. Blood chemistry findings and ECG recordings (including QT intervals) were similar on days 14 and 28 and were clinically insignificant. Agranulocytosis and seizures were not observed during the study.

DISCUSSION

This preliminary study suggests that coadministration of regular-strength grapefruit juice, 250 mL b.i.d., for 2 weeks does not significantly alter multiple-dose pharmacokinetics and pharmacodynamics of clozapine. This study, however, had several limitations. First, the juice was given at a fixed dose. It is unclear whether grapefruit juice at higher doses or after longer consumption periods could generate different results. Earlier studies[6,11] have suggested that higher doses of grapefruit juice may exert stronger inhibition of CYP3A4. Moreover, the doses of grapefruit juice also determine its effects on P-glycoprotein.[13] Second, this study lacked a parallel control group that received clozapine plus water throughout. Third, since the study was nonblind, the clinical ratings could be biased.

Although it improves the outcome of refractory schizophrenic patients, clozapine carries risks of adverse reactions,[17,34] including dose-related changes in vital signs, seizure thresholds,[17,34,35] and QT intervals in ECG.[36] Furthermore, a variety of drug-drug interactions have been reported with clozapine.[17–19,22] The impact of CYP3A4 inhibitors on clozapine disposition, however, appeared uncertain in antecedent studies.[37–40] The current study lends supports to the idea that CYP3A4 inhibitors do not influence clozapine metabolism. Likewise, in another study (N = 5, H.-Y.L., unpublished data, Sept. 2000), coadministration of 400 mg/day of ketoconazole (a CYP3A4 inhibitor) for 7 consecutive days failed to change single-dose clozapine pharmacokinetics. One reason is that enzymes other than CYP3A4 (such as CYP1A2 and CYP2C19) also mediate clozapine disposition.[17,18] These could result in the continued formation of norclozapine, clozapine *N*-oxide, and other clozapine metabolites despite the presence of grapefruit juice. Also, grapefruit juice inhibits CYP3A4 in the gut, but not in the liver; this phenomenon may further weaken its possible effects on clozapine metabolism.

In agreement with in vitro and animal studies,[16] our findings also suggest that clozapine is unlikely to be a substrate of P-glycoprotein. Therefore, factors that alter the activity of P-glycoprotein may not influence clozapine disposition. To date, very little is known about how drugs, diseases, aging, or genetic variations may affect P-glycoprotein or other transporters.[14,15] Nonetheless, ketoconazole, quinidine, verapamil and other calcium channel blockers, propranolol, and ritonavir have been shown to acutely inhibit the transport of substrates by P-glycoprotein.[14,15] Fluphenazine may also modulate P-glycoprotein activity to some extent.[14] Some medications that are substrates of CYP3A4 also appear to be P-glycoprotein substrates; however, these 2 characteristics do not always coincide.[14,15]

Clozapine-induced EEG slowing has been found to be a function of serum clozapine levels.[41] It is theoretically

possible that the EEG change may be more significantly related to brain clozapine levels than to serum clozapine levels. Since clozapine levels in the central nervous system (CNS) were unavailable in the present study, we could not test this hypothesis or directly evaluate the effects of grapefruit juice on CNS clozapine levels. Nonetheless, this study demonstrated that the prevalence of clozapine-related EEG slowing was similar before and after grapefruit juice coadministration.

A 5-year naturalistic study[42] revealed a trend increment in total serum cholesterol levels in clozapine-treated patients. Of interest, a 16-week crossover study[43] found that grapefruit pectin significantly decreases blood cholesterol in hypercholesterolemia patients. If further studies could confirm the safety of longer-term coadministration of grapefruit and clozapine, grapefruit could be utilized to reduce the risk or the severity of hypercholesterolemia in clozapine-treated patients.

It has been repeatedly recommended that patients who are taking drugs that are CYP3A4 substrates[18] be warned about the potential drug interactions with grapefruit.[1,5,44] In the current study, steady-state plasma levels, clinical efficacy, and side effect profiles of clozapine, a partial substrate of CYP3A4, were not altered by repeated ingestion of regular-strength grapefruit juice. Further studies with rigorous methodology and larger sample sizes are necessary to replicate the findings.

Drug names: clozapine (Clozaril and others), cyclosporine (Sandimmune and others), diazepam (Valium and others), fluvoxamine (Luvox), ketoconazole (Nizoral and others), lovastatin (Mevacor), midazolam (Versed and others), propranolol (Inderal and others), quinidine (Quinidex and others), ritonavir (Norvir), sertraline (Zoloft), triazolam (Halcion), verapamil (Isoptin and others).

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