Clinical Interaction Between Grapefruit Juice and Cyclosporine: Is There any Interest for the Hematologists?

To the Editor:

In the last few years a lot of reports dealt with pharmacokinetic interactions leading to elevated cyclosporine (CsA) blood concentrations. These interactions involve various drugs and food constituents, including antibiotics, antifungal agents, calcium antagonists, dietary lipids, and grapefruit juice.1,2 Grapefruit juice has been shown to significantly inhibit the gut wall cytochrome P 450 isoenzyme CYP 3A4, which is important in metabolism of CsA.3

The effect appears to be caused by the components of grapefruit juice, naringin, naringenin, or other flavonoids.4,5 The bioavailability of conventional CsA is low, with variable adsorption, clearance, and distribution; dosing, safe and effective use, and toxicity of the drug are still a matter of debate even though a better bioavailability has been observed with a new CsA microemulsion formulation.6 Recently, a study was presented7 on healthy adult volunteers, showing that coadministration of a defined dose of grapefruit juice could increase blood CsA concentration. A similar effect was observed in renal transplant recipients8 and also in patients with autoimmune rheumatologic diseases.9 However, it is still uncertain whether the effect of grapefruit juice may be sustained over time and whether it may contribute to maximize efficacy and minimize toxicity of CsA. So, we consider it useful to report on the satisfactory effect of grapefruit juice on blood CsA concentration and clinical outcome in four resistant, CsA-dependent, hematological patients followed for 9 months.

Four patients (age 20 to 69 years) with hematological immune disorders were treated: a female with autoimmune hemolytic anemia (AIHA), a female with idiopathic thrombocytopenic purpura (ITP), a male with AIHA in chronic lymphocytic leukemia (CLL), and a male with severe aplastic anemia (AA). With the exception of the AA patient, the other three patients were resistant to other immunosuppressive treatments and splenectomy, and the hematological remission was maintained with chronic administration of CsA for 13 to 58 months. Further details on these patients have been reported elsewhere.10 The AA patient was on CsA with water treatment for 3 months. Four patients (two AIHA women, one ITP woman, one AA man; age 28 to 62 years) having CsA only with water were followed for the same time as controls.

After informed consent, the grapefruit juice (250 mL) was coadministered orally with cyclosporine A capsules, outside the clinic. The drug daily dose (3 to 4 mg/kg to maintain the blood therapeutic values of 200 to 400 ng/mL) was administered simultaneously with the juice, half in the morning and half in the evening. Four patients (age 20 to 69 years) with hematological immune disorders were treated: a female with autoimmune hemolytic anemia (AIHA), a female with idiopathic thrombocytopenic purpura (ITP), a male with AIHA in chronic lymphocytic leukemia (CLL), and a male with severe aplastic anemia (AA). With the exception of the AA patient, the other three patients were resistant to other immunosuppressive treatments and splenectomy, and the hematological remission was maintained with chronic administration of CsA for 13 to 58 months. Further details on these patients have been reported elsewhere.10 The AA patient was on CsA with water treatment for 3 months. Four patients (two AIHA women, one ITP woman, one AA man; age 28 to 62 years) having CsA only with water were followed for the same time as controls.

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![Fig 1. Effect of coadministration of grapefruit juice and CsA on Hb and platelet (Plt) levels in four patients. CsA blood normal therapeutic values = 200 to 400 ng/mL.](https://ashpublications.org/blood/article-pdf/91/1/362/1415924/362.pdf)
in the evening. Two patients (with AIHA and AA) used commercially available grapefruit juice and the others (with ITP and AIHA + CLL) a juice obtained by a commercially available self-squeezed grapefruit.

The CsA blood concentration was monitored every 2 weeks by Sandimun-kit radioimmunoassay as well as blood pressure, glucose, serum creatinine, serum glutamic oxaloacetic, and pyruvic transaminase and lactate dehydrogenase levels. In all patients treated with CsA plus grapefruit juice, after 2 weeks of treatment we noted a progressive increase of CsA blood concentration and an increase of hemoglobin (Hb) and platelet levels; we also noted an increase in the white blood cell levels in the AA patient.

This allowed a reduction of CsA doses, especially in ITP patient (Fig 1). For all patients, the clinical outcome progressively improved (Fig 1). Neither nephrotoxicity nor other side effects were observed. The ITP patient, with drug requiring, CsA-dependent hypertension was also able to withdraw the antihypertensive drugs. In the control patients treated with CsA with water, the hematological remission was maintained over time with full CsA doses and without any possibility of CsA dose reduction.

Our data suggest that coadministration of CsA with grapefruit juice in drug-dependent hematological patients could increase CsA blood concentration and that the effect is sustained over time. This interaction, if unmonitored, is potentially dangerous, increasing toxicity of CsA. On the other hand it allows the reduction of daily required dose of drug, improving the clinical outcome on the whole with stable results and without side effects, at least in patients with hematological disorders. Moreover, the reduction of drug dosage can cut its side effects, as in one of our patients, as well as the cost of treatment.

We think that it would seem reasonable to warn the hematologists, the patients under long-term CsA treatment, and the pharmacists of this food-drug interaction.

Giovanni Emilia
Giuseppe Longo
Marcello Bertesi
Giovanna Gandini
Leonardo Ferrara
Chiara Valenti
Department of Medical Sciences
Section of Internal Medicine
University of Modena
Modena, Italy

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An Erythroid-Specific Exon Is Present in the Human Hexokinase Gene

To the Editor:

Human hexokinase type I (EC 2.7.1.1) is the predominant glucose-phosphorylating enzyme in red blood cells. By a number of methods it has been proved, and is now widely accepted, that this enzyme is largely heterogeneous and present in multiple molecular forms. Hexokinase subtypes have similar kinetic properties but a different age-dependent decay and a different intracellular distribution in reticulocytes.

It is presently unknown if the multiple hexokinase subtypes reflect posttranslational modifications or different gene products. We previously showed that, at least in human placenta, the heterogeneity of hexokinase type I is caused by the presence of truncate forms arising postsynthetically.

In the February issue of BLOOD, Murakami and Piomelli reported evidence for a red cell–specific hexokinase cDNA containing a unique sequence of 60 nucleotides at the beginning of the coding region. We have now identified this red cell–specific hexokinase sequence in the human genome and found that it is located 3.1 kb upstream from the somatic exon 1 (GenBank accession number AF016350). Determination of the splice-junction by direct sequencing confirmed the hypothesis that a true hexokinase isozyme may exist in humans, likely as a product of an alternative splicing event. However, human erythrocytes show a multiplicity of forms that cannot be explained only on the bases of two alternative hexokinase isozymes. Thus, the origin of hexokinase multiplicity remains at least in part to be determined.

Finally, we would like to note that expression of recombinant human hexokinase type I lacking the porin-binding domain results in an enzyme with normal kinetic and regulatory properties (Bianchi et al, submitted for publication). Thus, in cases of hexokinase mutations with altered enzymatic properties, the mutation must be searched for downstream of exon 1. This exon could instead confer stability to the enzyme by favoring binding to intracellular organelles and be responsible for enzyme defects with accelerated in vivo hexokinase decay.

Annamaria Ruzzo
Francesca Andreoni
Mauro Magnani
“G. Fornaini” Institute of Biological Chemistry
University of Urbino
Urbino, Italy