Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: comparison with ritonavir.


Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, and Tufts-New England Medical Center, Boston, Mass 02111, USA.

BACKGROUND AND OBJECTIVES: Acute ingestion of usual quantities of grapefruit juice produces inhibition of enteric cytochrome P450 (CYP) 3A enzymes, causing pharmacokinetic interactions with a number of drugs. However, the effect of extended exposure to grapefruit juice on CYP3A activity is not established.

METHODS: Triazolam, a CYP3A index compound, was administered to 3 cohorts of volunteers (n = 6-7 per group) on 4 occasions (trials 1-4), as follows: 1 day prior to co-treatment initiation, at the beginning and end of co-treatment, and 3 days after co-treatment discontinuation. The 3 co-treatments (daily administration for 10 consecutive days) were: 300 mL grapefruit juice, 400 mg ritonavir, or 300 mL water.

RESULTS: Grapefruit juice co-treatment (trial 2) increased the triazolam area under the plasma concentration curve by 50% compared to the trial 1 control (15.1 +/- 7.6 ng/mL.h versus 10.0 +/- 3.5 ng/mL.h, P < .05), but the half-life was not changed. Effects of acute and extended exposure to grapefruit juice (trials 2 and 3) were similar, and produced augmentation in benzodiazepine agonist effects measured by the Digit Symbol Substitution Test and electroencephalographic beta amplitude. Kinetic and dynamic effects reverted to baseline (trial 1) values at 3 days after grapefruit juice discontinuation (trial 4). Ritonavir caused a more than 20-fold increase in the triazolam area under the plasma concentration curve during trial 2 (553 +/- 422 ng/mL.h) and trial 3 (287 +/- 299 ng/mL.h) compared to the trial 1 control (13.3 +/- 16.3 ng/mL.h) (P < .05 for both comparisons); Digit Symbol Substitution Test and electroencephalographic pharmacodynamics increased in parallel. During trial 4, triazolam kinetics reverted close to trial 1 values, with no evidence of induction. Triazolam kinetics were not altered by water co-treatment.

CONCLUSION: Acute and extended exposure to grapefruit juice produces quantitatively similar inhibition of enteric, but not hepatic, CYP3A. Recovery is complete within 3 days after grapefruit juice discontinuation. Ritonavir greatly inhibits both enteric and hepatic CYP3A. With extended exposure to ritonavir, inhibition is the predominant effect, and recovery to baseline is nearly complete 3 days after ritonavir discontinuation.

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Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4