

Effect of **grapefruit juice** dose on **grapefruit juice-triazolam** interaction: repeated consumption prolongs **triazolam** half-life.

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OBJECTIVE: **Grapefruit juice** inhibits CYP3A4-mediated metabolism of several drugs during first pass. In this study, the effect of **grapefruit juice** dose on the extent of **grapefruit juice-triazolam** interaction was investigated. **METHODS:** In a randomised, four-phase, crossover study, 12 healthy volunteers received 0.25 mg **triazolam** with water, with 200 ml normal-strength or double-strength **grapefruit juice** or, on the third day of multiple-dose [three times daily (t.i.d.)] administration of double-strength **grapefruit juice**. Timed blood samples were collected up to 23 h after dosing, and the effects of **triazolam** were measured with four psychomotor tests up to 10 h after dosing. **RESULTS:** The area under the plasma **triazolam** concentration time curve (AUC(0-infinity)) was increased by 53% (P < 0.01), 49% (P < 0.01) and 143% (P < 0.001) by a single dose of normal-strength, a single dose of double-strength and multiple-dose administration of double-strength **grapefruit juice**, respectively. The peak plasma concentration (C_{max}) of **triazolam** was increased by about 40% by a single dose of normal-strength **grapefruit juice** (P < 0.01) and multiple-dose **grapefruit juice** (P < 0.01) and by 25% by a single dose of double-strength **grapefruit juice** (P < 0.05). The elimination half-life (t(1/2)) of **triazolam** was prolonged by 54% during the multiple-dose **grapefruit juice** phase (P < 0.001). A significant increase in the pharmacodynamic effects of **triazolam** was seen during the multiple-dose **grapefruit juice** phase in the digit symbol substitution test (DSST, P < 0.05), in subjective overall drug effect (P < 0.05) and in subjective drowsiness (P < 0.05).

CONCLUSIONS: Even one glass of **grapefruit juice** increases plasma **triazolam** concentrations, but repeated consumption of **grapefruit juice** produces a significantly greater increase in **triazolam** concentrations than one glass of **juice**. The t(1/2) of **triazolam** is prolonged by repeated consumption of **grapefruit juice**, probably due to inhibition of hepatic CYP3A4 activity.

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
<ul style="list-style-type: none"> • Anti-Anxiety Agents, Benzodiazepine [pharmacokinetics] • Beverages • Citrus • Triazolam [pharmacokinetics] 	<ul style="list-style-type: none"> • Adult • Anti-Anxiety Agents, Benzodiazepine [blood] • Biological Availability • Cross-Over Studies • Dose-Response Relationship, Drug • Female • Half-Life • Human • Logistic Models • Male • Psychomotor Performance [drug effects] • Support, Non-U.S. Gov't • Triazolam [blood] 	<ul style="list-style-type: none"> • 0 (Anti-Anxiety Agents, Benzodiazepine) • 28911-01-5 (Triazolam)