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Grapefruit juice can increase the plasma concentrations of oral methylprednisolone

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Abstract *Objective*: To investigate whether the pharmacokinetics of orally administered methylprednisolone and plasma cortisol concentrations are affected by administration of grapefruit juice.
Methods: In a randomised, two-phase, cross-over study, ten healthy subjects received either 200 ml double-strength grapefruit juice or water three times a day for 2 days. On day 3, 16 mg methylprednisolone was given orally with 200 ml grapefruit juice or water. Additionally, 200 ml grapefruit juice or water was ingested 0.5 h and 1.5 h after methylprednisolone administration. Plasma concentrations of methylprednisolone and cortisol were determined using liquid chromatography/mass spectrometry (LC/MS/MS) over a 47-h period.
Results: Grapefruit juice increased the total area under the plasma methylprednisolone concentration–time curve ($AUC_{0-\infty}$) by 75% ($P < 0.001$) and the elimination half-life ($t_{1/2}$) of methylprednisolone by 35% ($P < 0.001$). The peak plasma concentration of methylprednisolone (C_{max}) was increased by 27% ($P < 0.01$). Grapefruit juice delayed the time to the C_{max} from 2.0 h to 3.0 h ($P < 0.05$). There was no significant difference in the plasma cortisol concentrations, measured after methylprednisolone administration, between the water and grapefruit juice phases. However, grapefruit juice slightly decreased the morning plasma cortisol concentrations before methylprednisolone administration ($P < 0.05$).
Conclusions: Grapefruit juice given in high amounts moderately increases the $AUC_{0-\infty}$ and $t_{1/2}$ of oral methylprednisolone. The increase in $t_{1/2}$ suggests that grapefruit juice can affect the systemic methylprednisolone metabolism. The clinical significance of the grapefruit juice–methylprednisolone interaction is small, but in some sensitive subjects high doses of grapefruit juice might enhance the effects of oral methylprednisolone.

Key words Methylprednisolone · Grapefruit juice · Interaction

Introduction

Grapefruit juice considerably increases the oral bioavailability of dihydropyridine calcium channel blockers, such as felodipine, nifedipine and nisoldipine [1, 2]. In addition, grapefruit juice increases the bioavailability of many other cytochrome P_{450} 3A4 (CYP3A4) substrates, such as terfenadine, midazolam and simvastatin [3, 4, 5]. The increase in bioavailability by grapefruit juice may also enhance the pharmacodynamic effects of the drug (e.g. midazolam, terfenadine) [3, 4]. The observed interaction can be greater after repeated consumption than after a single glass of grapefruit juice [6, 7].

CYP3A4 is probably involved in the biotransformation of methylprednisolone, because potent inhibitors of CYP3A4 (troleandomycin, ketoconazole, itraconazole) increase its plasma concentrations [8, 9, 10, 11]. The main purpose of this study was to evaluate whether the repeated consumption of grapefruit juice can affect the pharmacokinetics of oral methylprednisolone. An interaction between grapefruit juice and oral methylprednisolone could potentially enhance the effects of this widely used glucocorticoid.

Materials and methods

Subjects

Ten young, healthy subjects were enrolled in this study after giving written informed consent (Table 1). Before participation, the subjects underwent a medical screening including medical history, physical examination and routine laboratory tests to ensure that all

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Table 1 Characteristics of the study subjects

Subject number	Gender	Age (years)	Weight (kg)
1	Male	21	66
2	Male	25	77
3	Male	23	64
4	Male	20	80
5	Female	21	57
6	Male	20	62
7	Male	25	70
8	Female	19	68
9	Male	21	73
10	Male	20	63

the subjects were in good health. None of the subjects was a smoker or used continuous medication (including oral contraceptives). Grapefruit products, excluding the grapefruit juice given by the investigators, and use of any other drugs were prohibited during the study period, starting 2 weeks before the first study day.

Study design

A randomised cross-over study design with two phases separated by a wash-out period of 4 weeks was used. The study subjects drank 200 ml double-strength grapefruit juice [12 ounces (335 ml) Minute Maid frozen concentrated grapefruit juice, Coca Cola Foods, Houston, Tex.] or 200 ml water three times a day (at 0700, 1200 and 2000 hours) for 2 days. On day 3, after an overnight fast, each subject was given 16 mg methylprednisolone orally (Solomet 16 mg tablet, Orion Pharma, Finland) with 200 ml double-strength grapefruit juice or water at 0900 hours. In addition, 200 ml grapefruit juice or water was given 0.5 h and 1.5 h after methylprednisolone administration. A light standard meal was served 2 h and 10 h and a standard lunch 6 h after methylprednisolone administration. The study protocol was approved by the ethics committee of the Department of Clinical Pharmacology, University of Helsinki (Helsinki, Finland) and the Finnish National Agency for Medicines.

Blood sampling and determination of plasma drug and cortisol concentrations

Timed blood samples (10 ml each) were drawn into tubes that contained ethylene diamine tetraacetic acid (EDTA) before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 23 and 47 h after methylprednisolone administration. Plasma was separated within 30 min and stored at −40 °C until analysis. Plasma methylprednisolone and cortisol concentrations were determined using liquid chromatography-ionspray-tandem mass spectrometry with use of the PE SCIEX API 3000 LC/MS/MS system (Sciex Division of MDS Inc, Toronto, Canada), using dexamethasone as an internal standard [12, 13]. The quantification limit was 0.5 ng/ml for both methylprednisolone and cortisol. The interday coefficient of variation (CV) for methylprednisolone was 6.3% at 4.3 ng/ml ($n = 4$), 2.3% at 25 ng/ml ($n = 4$) and 3.6% at 118 ng/ml ($n = 4$). The interday CV for cortisol was 1.2% at 4.1 ng/ml ($n = 5$), 6.1% at 25 ng/ml ($n = 5$) and 4.3% at 123 ng/ml ($n = 5$).

Pharmacokinetics

The pharmacokinetics of methylprednisolone were characterised by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), area under the plasma methylprednisolone concentration–time curve ($AUC_{0-\infty}$) and elimination half-life ($t_{1/2}$) [14]. The C_{max} and t_{max} were obtained directly from the data. The terminal log-linear phase of the plasma concentration–time curve was visually identified for each subject. The elimination rate constant (k_{el}) was determined using linear regression analysis of the log-linear part of the curve. The $AUC_{0-\infty}$ was calculated using the trapezoidal rule (using the log trapezoidal rule beyond the C_{max}), with extrapolation to infinity by dividing the last measured concentration by k_{el}. The $t_{1/2}$ was calculated from the equation $t_{1/2} = \ln 2/k_{el}$.

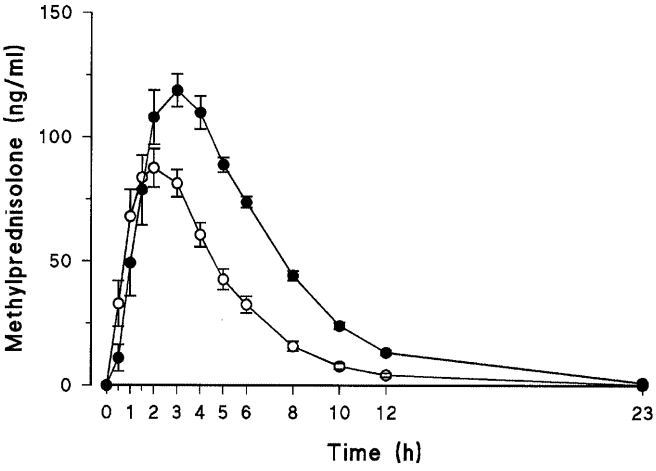

Fig. 1 Plasma concentrations of methylprednisolone in ten subjects (means with SEM) after an oral dose of 16 mg methylprednisolone, after ingestion of 200 ml grapefruit juice (*solid circles*) or water (*open circles*) three times a day for 2 days and on day 3 with methylprednisolone and 0.5 h and 1.5 h later

Plasma cortisol concentrations

The effect of methylprednisolone on endogenous cortisol secretion was evaluated by measuring the morning plasma cortisol concentration (normal range in the morning, 50–250 ng/ml) on the third day (i.e. before the intake of methylprednisolone) and on the following 2 days (i.e. 23 h and 47 h after the administration of methylprednisolone). In addition, the $AUC_{0-12\ h}$ of cortisol was calculated using the linear trapezoidal rule.

Statistical analysis

Results are expressed as mean values ± SD, except for t_{max} which is presented as median with range. In Fig. 1, the data are expressed as means with SEM for clarity. The pharmacokinetic variables of methylprednisolone, plasma cortisol concentrations at 0, 23 and 47 h and the $AUC_{0-12\ h}$ of cortisol between the phases were compared using a paired (two-tailed) *t*-test. The Wilcoxon test was used for analysis of t_{max}. The data were analysed using the statistical program Systat for Windows, version 6.0.1 (SPSS Inc., Chicago, Ill.). The level of significance was $P < 0.05$.

Results

Methylprednisolone

Grapefruit juice slightly delayed the absorption of methylprednisolone and considerably increased its plasma concentrations from 2 h onwards (Fig. 1). The $AUC_{0-\infty}$ of methylprednisolone was increased by 75% (range 42–110%; $P < 0.001$) by grapefruit juice compared with water (Fig. 1, Fig. 2 and Table 2). An increase in the $AUC_{0-\infty}$ of methylprednisolone was observed in all subjects (Fig. 2). The C_{max} of methyl-

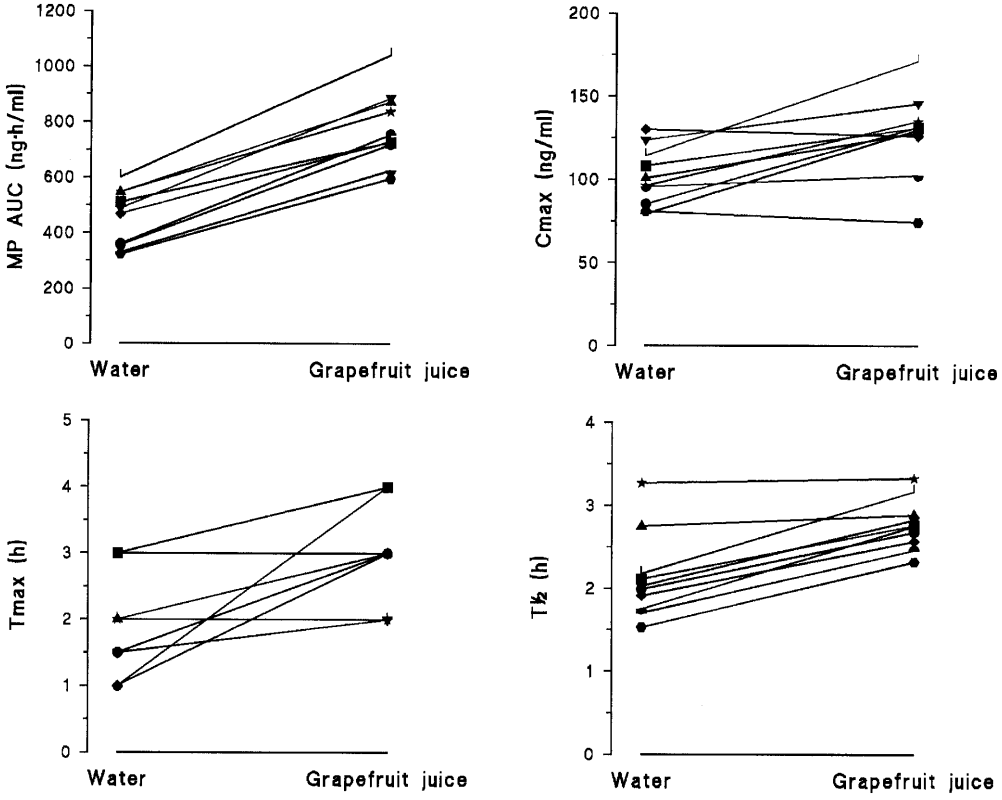

Fig. 2 The individual area under the curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), time to C_{max} (t_{max}) and elimination half-life ($t_{1/2}$) values during the water and grapefruit juice phases in ten subjects after an oral dose of 16 mg methylprednisolone (MP)

prednisolone was increased by 27% (range – 8% to 64%; $P < 0.01$) and the $t_{1/2}$ by 35% (range 2–57%; $P < 0.001$) (Fig. 2, Table 2). The t_{max} of methylprednisolone was prolonged from 2.0 h to 3.0 h ($P < 0.05$) by grapefruit juice.

Cortisol

The $AUC_{0-12\ h}$ of cortisol was slightly greater during the grapefruit juice phase than during the water phase (500 ± 165 ng h/ml versus 453 ± 103 ng h/ml, $P = 0.08$). However, the plasma cortisol concentration measured in the morning of the third study day (before administration of methylprednisolone) was significantly lower ($P < 0.05$) during the grapefruit juice phase than during the water phase (140 ± 47 ng/ml versus 169 ± 37 ng/ml; Fig. 3). Furthermore, the morning plasma cortisol measured 23 h after the administration of methyl-

Table 2 The pharmacokinetic variables of methylprednisolone in ten subjects after ingestion of 16 mg methylprednisolone with water or grapefruit juice. C_{max} peak plasma concentration; $t_{1/2}$ elimination half-life; t_{max} time to C_{max}; *AUC* area under the curve; *CI* confidence interval. Data are mean values ± SD. t_{max} is given as median (range)

Variable	Water phase (control)	Grapefruit juice phase
C_{max} (ng/ml)	101 ± 1	128 ± 25**
Percentage of control (95% CI)	100	127 (109–145)
t_{max} (h)	2.0 (1.0–3.0)	3.0 (2.0–4.0)*
$t_{1/2}$ (h)	2.1 ± 0.5	2.8 ± 0.3***
Percentage of control (95% CI)	100	135 (122–148)
$AUC_{0-\infty}$ (ng h/ml)	453 ± 103	780 ± 133***
Percentage of control (95% CI)	100	175 (159–191)

*$P < 0.05$ vs control phase (water)
**$P < 0.01$ vs control phase (water)
***$P < 0.001$ vs control phase (water)

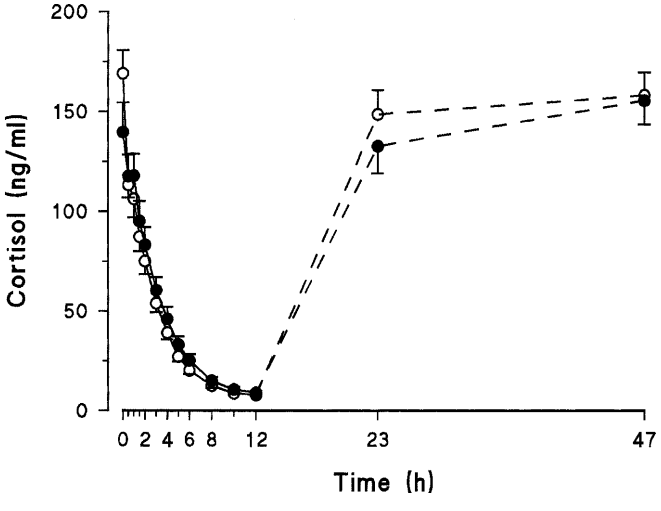

Fig. 3 Plasma concentrations of cortisol in ten subjects (means with SEM) after an oral dose of 16 mg methylprednisolone, after ingestion of 200 ml grapefruit juice (*solid circles*) or water (*open circles*) three times a day for 2 days and on day 3 with methylprednisolone and 0.5 h and 1.5 h later

prednisolone was slightly lower during the grapefruit juice phase than during the water phase (133 ng/ml ± 43 versus 149 ± 39 ng/ml, $P = 0.09$).

Discussion

In the present study, grapefruit juice increased the plasma concentrations of oral methylprednisolone, increasing its $AUC_{0-\infty}$ and C_{max} by 75% and 27%, respectively. In addition, grapefruit juice increased the t_{max} and $t_{1/2}$ of methylprednisolone.

The oral bioavailability of many CYP3A4 substrates increases by concomitant use of grapefruit juice [4, 15]. Although both the enterocytes of the small bowel and the hepatocytes express CYP3A4 [16, 17], recent studies indicate that the grapefruit juice–drug interaction results mainly from inhibition of the first-pass metabolism in the gut wall [15, 18]. Furthermore, in a recent study, grapefruit juice decreased the expression of intestinal CYP3A4 without affecting the liver CYP3A4 activity, as measured using the erythromycin breath test [19]. As CYP3A4 probably has an important role in the metabolism of methylprednisolone [11], the observed increases in the C_{max} and $AUC_{0-\infty}$ of methylprednisolone by grapefruit juice can partly be explained by inhibition of the CYP3A4-mediated intestinal first-pass metabolism of methylprednisolone. One possible explanation could be inhibition of the intestinal P-glycoprotein by grapefruit juice. However, the data concerning the effect of grapefruit juice on the intestinal P-glycoprotein are somewhat discrepant [19, 20, 21].

The $t_{1/2}$ of methylprednisolone was slightly but significantly increased by grapefruit juice. This suggests that the systemic metabolism of methylprednisolone was also inhibited by grapefruit juice, assuming that grapefruit juice did not alter the volume of distribution of methylprednisolone. According to a recent study, high amounts of grapefruit juice can affect both presystemic and systemic metabolism of oral midazolam, a well-known marker of CYP3A4 activity [22]. Furthermore, grapefruit juice lowers the urinary cortisone/cortisol ratio in some sensitive subjects, suggesting inhibition of the 11β-hydroxysteroid dehydrogenase enzyme [23]. Thus, several lines of evidence suggest that high amounts of grapefruit juice can affect also the systemic drug metabolism.

The endogenous cortisol synthesis shows a diurnal variation, with peak cortisol concentrations occurring early in the morning. In the present study, ingestion of (double-strength) grapefruit juice three times a day for 2 days slightly decreased the morning plasma cortisol concentration, measured in the morning of the third study day before administration of methylprednisolone. In contrast, after the ingestion of 16 mg methylprednisolone, the $AUC_{0-12\,h}$ of cortisol tended to be greater during the grapefruit juice phase than during the water phase. It should be noted, however, that the changes in the plasma cortisol concentrations observed in the present study were minor and may have been caused by chance.

The concomitant use of itraconazole and methylprednisolone can result in glucocorticoid-related adverse effects (e.g. diabetes mellitus and myopathy) [24]. Itraconazole (200 mg daily for 4 days) increased the $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ of oral methylprednisolone 3.9-, 1.9- and 2.4-fold, respectively [11]. The interaction of oral methylprednisolone with grapefruit juice is clearly smaller than that observed with itraconazole. Furthermore, grapefruit juice did not alter the pharmacokinetics of prednisolone in transplant patients after oral administration of prednisone [25].

In conclusion, grapefruit juice taken in high amounts moderately increases the $AUC_{0-\infty}$ and $t_{1/2}$ of oral methylprednisolone. The increase in $t_{1/2}$ suggests that grapefruit juice can affect the systemic methylprednisolone metabolism. The clinical significance of the grapefruit juice–methylprednisolone interaction is small, but in sensitive subjects high doses of grapefruit juice might enhance the effects of oral methylprednisolone.

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