

## Effects of Grapefruit Juice Consumption on Pharmacokinetics of Low Dose Simvastatin: Cross-over Study with a Review of the Literature

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### Abstract

The effects of consumption of grapefruit juice on the pharmacokinetics of conventional low-dose simvastatin in Japan were investigated. In a randomized cross-over study with two phases, 10 healthy volunteers ingested grapefruit juice 400ml or water for 2 days. On day 3, a single 5mg dose of simvastatin was administered with grapefruit juice 200ml or water. Plasma concentrations of HMG-CoA reductase inhibitor were determined up to 8 h thereafter. Grapefruit juice increased the area under the plasma concentration-time curves from 0 to 8 h of total HMG-CoA reductase inhibitor 1.7-fold ( $p=0.002$ ) and that of active HMG-CoA reductase inhibitor 1.7-fold ( $p=0.024$ ). However, the peak concentrations ( $C_{max}$ ) and  $T_{max}$  of total and active HMG-CoA reductase inhibitors were not significant influenced. Consumption of grapefruit juice with low-dose simvastatin thus resulted in mild increase of the plasma HMG-CoA reductase inhibitor, so that the pharmacokinetic interaction can be labeled as of weak CYP3A type.

### Introduction

Grapefruit juice has been reported to increase plasma concentrations of calcium channel blockers [1], some HMG-CoA reductase inhibitors [2-6] and other pharmaceutical drugs, with reported selective downregulation of CYP3A4 in the duodenal epithelium where this enzyme is localized [7]. Repeated consumption of high quantities of the juice is reported to elevate AUC values of lovastatin and simvastatin over 10 fold [2,3] and even one glass of grapefruit juice (200 ml), taken daily, was found to increase the area under the plasma concentration-time curves from 0-24 h [AUC (0-24)] for simvastatin 3.6 fold and for simvastatin acid 3.3 fold. The peak concentrations ( $C_{max}$ ) were increased 3.9 fold and 4.3 fold, respectively [5]. In Japan, the conventional dose of statin (simvastatin) applied (5 mg) is much smaller than in Western countries (40-60mg) [3-5]. In the present study, effects of consumption of grapefruit juice on pharmacokinetics with this low dose were assessed.

### Materials and Methods

#### Subjects

Ten healthy volunteers (5 men and 5 women: age range 23-35 years; weight range 43-84 kg) participated in the study. Each subject was ascertained to be in good health with reference to medical history, clinical examination, and routine laboratory testing. None were using any continuous medication, and all of them were non-smokers. The use of the grapefruit was controlled during the study according to the protocol.

#### Study design

A randomized crossover study design with two phases was employed with an interval of 2 weeks. The volunteers ingested 200ml of standard grapefruit juice (Morinaga, Tokyo, Japan) or water twice a day at 7:00 and 20:00 for two days. On the third day they received 5 mg simvastatin (Lipovas, MSD, Tokyo, Japan) at 8:00 with 200ml grapefruit juice or water. The volunteers fasted overnight before administration of simvastatin, and standardized warm meal was served 3 h and a standardized warm light meal 7 h after simvastatin intake. The subjects were not allowed to drink coffee, tea, or cola during the study days.

### Blood sampling

On the third study day, a plastic cannula was inserted into a forearm vein of each participant and was kept patent with an obturator. Timed blood samples were drawn into ethylenediaminetetraacetic acid (EDTA)-containing 2.5 ml tubes before the administration of simvastatin and 1, 2, 4, and 8 h later. Plasma was separated within 30 min and stored at  $-80^{\circ}\text{C}$  until analysis.

### Determination of active and total HMG-CoA reductase inhibitors concentrations

The HMG-CoA reductase inhibitory activity of the plasma samples was measured by enzymatic activity assay [8]. All plasma inhibitor concentrations are expressed in simvastatin acid equivalents. HMA-CoA reductase inhibitory activity in plasma was measured before and after base hydrolysis. The corresponding plasma concentration values are referred to as active and total HMG-CoA reductase inhibitor concentrations, respectively.

### Pharmacokinetic analysis

The  $C_{max}$  and  $T_{max}$  of total HMG-CoA reductase inhibitors and active HMG-CoA reductase inhibitors were obtained directly. The terminal log-linear phase of the plasma concentration-time curve was visually identified for each and the elimination rate constant ( $k_e$ ) was determined by linear regression analysis. The area under the plasma concentration-time curve up to the last quantified data point [AUC (0-8 h)] was calculated by the linear trapezoidal rule and the elimination half-life ( $T_{1/2}$ ) was determined by the equation.

$$= \ln 2 / k_e$$

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## Statistical analysis

The data are expressed as mean value±SD, except for  $T_{max}$ , which is presented as median with range. For all variables, except for  $T_{max}$ , 95% confidence intervals (CI) were calculated for the mean difference between water and grapefruit juice phases. Data were analysed with the Student t test (two-tailed) for paired values or, in case of  $T_{max}$  by the Wilcoxon test. The statistical program Systat for Windows was for all analyses, with differences considered statistically significant at  $p < 0.05$ .

## Results

### Total HMG-CoA reductase inhibitors

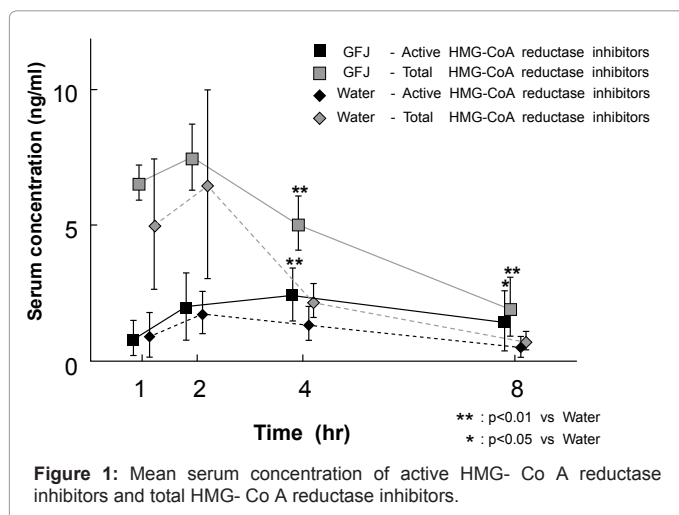
Grapefruit juice considerably increased plasma concentrations of total HMG-CoA reductase inhibitors in each subject (Figure 1 and Table 1). The mean AUC (0-8 h) of total HMG-CoA reductase inhibitors was increased 1.7-fold ( $p = 0.002$ ) by ingestion of grapefruit juice compared with water (control). The mean serum concentration of total HMG-CoA reductase inhibitors after 4h and 8h was also increased ( $p < 0.01$ ) (Figure 1), but there were no statistically significant changes in the mean  $C_{max}$  and  $T_{max}$  of total HMG-CoA reductase inhibitors (Table 1).

### Active HMG-CoA reductase inhibitors

Grapefruit juice considerably increased plasma concentrations of active HMG-CoA reductase inhibitors in each subject (Figure 1 and Table 1). The mean AUC (0-8 h) of active HMG-CoA reductase inhibitors was increased 1.7-fold ( $p = 0.024$ ) and the mean serum concentrations of active HMG-CoA reductase inhibitors were elevated after both 4 h ( $p < 0.01$ ) and 8 h ( $p < 0.05$ ) (Figure 1). There were no statistically significant changes in the mean  $C_{max}$  and  $T_{max}$  of active HMG-CoA reductase inhibitors.

## Discussion

Simvastatin, lovastatin, and atorvastatin resemble each other in their sensitivity regarding interaction with CYP3A4 inhibitors. Lown et al. [2] first reported that grapefruit juice selectively down-regulates CYP3A4 in the small intestine, without any effects on liver CYP3A4. Thereby, grapefruit juice should not be consumed concomitantly with statins which need CYP3A4 for metabolism. In Japan, low- the conventional dose of simvastatin (5 mg) is used conventionally, very much less than that in other countries (40-60 mg) because Japanese patients are more sensitive to the drug. The Japan Lipid Intervention Trial (J-LIT) study,



		Water	GFJ	
		mean ±SD	mean ±SD	p-value
Active HMG-CoA reductase inhibitors				
$C_{max}$	(ng/mL)	1.94 ±0.69	2.73 ±1.10	NS
$T_{max}$	(hr)	2.3 ±0.1	3.6 ±1.8	NS
AUC	(0-8hr)	8.7 ±3.7	14.5 ±6.3	0.024
Total HMG-CoA reductase inhibitors				
$C_{max}$	(ng/mL)	7.11 ±3.17	8.54 ±2.89	NS
$T_{max}$	(hr)	1.5 ±0.5	1.8 ±0.9	NS
AUC	(0-8hr)	22.9 ±6.7	38.2 ±11.2	0.002

Table 1: Pharmacokinetic parameters of active HMG-CoA reductase inhibitors and total HMG-CoA reductase inhibitors.

Simvastatin/ Grapefruit juice/ day	$C_{max}$		AUC	
	W/G-Active	W/G-Total	W/G-Active	W/G-Total
	ng/ml (p)		ng/ml (p)	
60mg/1200ml (3)	3.1/ 20.3	15.6/ 147.0	21.7/ 147.0	46.6/ 752
	(p<0.001)		(p<0.01)	(p<0.05)
40mg/1200ml (4)	3.9/ 19.6	9.3/ 112.0	24.9/ 114.0	27.8/ 373.0
	(p<0.001)		(p<0.001)	
40mg/200ml (5)	2.6/ 11.1	7.3/ 28.5	18.5/ 62.0	31.6/ 112.5
	(p<0.001)		(p<0.001)	

W: water group, G: grapefruit juice group, Active: concentration of active simvastatin acid, Total: concentration of total simvastatin  
Active Inhibitors\*: Active HMG-CoA reductase inhibitors  
Total Inhibitors\*: Total HMG-CoA reductase inhibitors  
Ng-eq/ml\*\* refers to the nanogram equivalents of simvastatin acid

Table 2: Review of the literature measuring active and total simvastatin level with regard to interaction of grapefruit juice with simvastatin.

Simvastatin/ Grapefruit juice/day	$C_{max}$		AUC	
	W/G-Active	W/G-Total	W/G-Active	W/G-Total
	Inhibitors*		Inhibitors*	
	ng-eq/ml** (p)		ng-eq/ml ** (p)	
60mg/1200m (3)	21.0/ 26.8	86.7/ 159	88.0/ 213	243/ 862
	(p<0.05)		(p<0.01)	
5mg/ 400ml (present series)	1.9/ 2.7	7.1/ 8.5	8.7/ 14.5	22.9/ 38.2
	(NS)		(p=0.024)	(p=0.002)

W: water group, G: grapefruit juice group, Active Inhibitors\*: active HMG-CoA reductase inhibitors, Total Inhibitors\*: total HMG-CoA reductase inhibitors  
Ng-eq/ml\*\* refers to the nanogram equivalents of simvastatin acid

Table 3: Review of the literature measuring HMG-CoA reductase inhibitors level with regard to interaction of grapefruit juice with simvastatin.

a nationwide cohort study, showed 5mg/ day to effectively control the serum total cholesterol and low density lipoprotein-cholesterol concentrations by reducing them by approximately 20% on average in hypercholesterolemic Japanese patients, a reduction that corresponds to the effect of 20mg/day in Western studies [9]. The effect of regular consumption of grapefruit on the pharmacokinetics of low-dose of simvastatin has not attracted attention in the past (Table 2)[3-5]. The With a high-dose (40mg) of simvastatin, where even a once daily a glass of grapefruit juice (200 ml) has been reported to increase simvastatin and simvastatin acid AUC 3.4-3.6 fold and  $C_{max}$  3.9-4.3 fold [5] or and high quantities of grapefruit juice (1200 ml/day) result in much greater levels for AUC (4.6-13.4 fold) and  $C_{max}$  (5.0-12.0 fold) [3,4].

Lilja et al. [3] has measured also HMG-CoA reductase inhibitory activity. They reported grapefruit juice significantly increased the serum concentrations of HMG-CoA reductase inhibitors (Table 3), but the effect was less than that on serum simvastatin and simvastatin acid (Table 2). The mean AUC of active inhibitors was increased 2.4-

fold ( $p < 0.01$ ) by grapefruit juice (Table 3). The mean  $C_{max}$  of total inhibitors was increased 1.8-fold ( $p < 0.01$ ) and the mean AUC was increased 3.6-fold. The data from the present study also, the enzyme inhibition assay, clearly indicate that even 5mg simvastatin with grapefruit juice twice daily (total: 400 ml) increases the mean AUC of active and total inhibitors (1.7 fold). Liu et al reported [8] the enzyme inhibition assay, which measures overall inhibitory activity from active and potentially active metabolites, is therefore, a preferred assay method for pharmacokinetic, bioavailability, and drug interaction studies. The FDA recommends that a 2-5 fold increase in AUC is moderate and most likely to be without any clinical relevance, while an increase  $> 5$  points indicates a severe interaction which will have clinical consequences. Between 1.25- and 2-fold, it can be labeled as of weak CYP3A inhibitor type [10]. Consumption of grapefruit juice (400 ml/day) with low-dose simvastatin (5 mg) caused a mild increase (1.7 fold) of the plasma HMG-CoA reductase inhibitor, so that the pharmacokinetic interaction can be labeled as of weak CYP3A inhibitor type. A rise in the actual in vivo dose of simvastatin has reported to increase the risk of skeletal muscle toxicity [11], myopathy or rhabdomyolysis occurring at incidences of 0.02%, 0.08%, and 0.53%, respectively, with 20, 40, and 80 mg daily, with high dose simvastatin at 80mg in another study [12], muscle toxicity not appear even with an AUC of 190 ng/ml for active simvastatin and 568 ng/ml for total simvastatin. The  $C_{max}$  of active simvastatin acid is 43 ng/ml and total simvastatin is 179 ng/ml. In the present study, low dose of simvastatin with regular consumption of grapefruit juice, the AUC of active HMG-CoA reductase inhibitors was 14.5 ng eq/ml and total HMG-CoA reductase inhibitors was 38.2 ng eq/ml, with  $C_{max}$  values of 2.73 ng/ml and 8.54 ng eq/ml, respectively. Low dose of simvastatin with regular consumption of grapefruit juice did not induce the high level of the active and total HMG-CoA reductase inhibitors compared with high dose of simvastatin [3] because the control serum value was low. The serum pharmacokinetic our data of 5 mg oral doses of simvastatin concomitant with 400 ml grapefruit juice corresponded to almost 1/3rd [13] to 1/5th [14] of the HMG-CoA reductase inhibitory activity which has been already reported with a 40 mg oral dose of simvastatin only. The risk of skeletal muscle toxicity should therefore be limited for patients taking a low dose of simvastatin concomitant with regular consumption of grapefruit juice.

The authors declared no conflict of interest.

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