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Effects of grapefruit juice on the absorption of levothyroxine

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Aims
Our aim was to study the effect of grapefruit juice on the pharmacokinetics of levothyroxine.

Methods
In a randomized cross-over study with two phases, 10 healthy subjects ingested 200 ml grapefruit juice or water (control) three times daily for 2 days. On day 3, a single 600 μg dose of levothyroxine was administered with 200 ml grapefruit juice or water, which was also ingested 1 h before and 1 h after levothyroxine. Serum concentrations of total thyroxine (T4) and thyroid-stimulating hormone (TSH) were measured up to 24 h.

Results
Grapefruit juice decreased slightly (11%; $P < 0.01$) the maximal increase of T4 concentration after ingestion of levothyroxine from 66.4 nmol l^{-1} to 59.4 nmol l^{-1} (95% CI on the difference −11.3, −2.7). The incremental areas under the serum T4 concentration-time curve (dAUC) during the first 4 and 6 h were also decreased slightly: dAUC(0,4 h) by 13% ($P < 0.05$), from 195 nmol l^{-1} h to 169 nmol l^{-1} h (95% CI −51, −1) and dAUC(0,6 h) by 9% ($P = 0.085$), from 298 nmol l^{-1} h to 271 nmol l^{-1} h (95% CI −58, 4). The decrease in the serum concentration of TSH (1.25 mU l^{-1}) measured 24 h after ingestion of levothyroxine, was not altered by grapefruit juice.

Conclusions
Grapefruit juice may slightly delay the absorption of levothyroxine, but it seems to have only a minor effect on its bioavailability. Accordingly, the clinical relevance of the grapefruit juice-levothyroxine interaction is likely to be small.

Introduction

Grapefruit juice increases the plasma concentrations of several drugs that are substrates for CYP3A4 [1], for example, felodipine [2], cyclosporin [3] and simvastatin [4]. The mechanism of these interactions is mainly inhibition of intestinal CYP3A4 activity, although repeated doses of grapefruit juice may also inhibit the activity of hepatic CYP3A4 [5]. Recently, grapefruit juice has been reported to decrease the plasma concentrations of some drugs, for example fexofenadine [6] and celiprolol [7], possibly by inhibiting intestinal uptake transporters [6].

Levothyroxine is widely used for the replacement of endogenous hormone in hypothyroidism and for suppressive therapy of thyroid neoplasia. After oral administration, approximately 70–80% of levothyroxine is absorbed [8]. Concomitant medication with cholestyramine [9], sucralfate [10], ferrous sulphate [11] and aluminium hydroxide [12] has been shown to

reduce its absorption, as have active charcoal and dietary fibre [13]. The mechanism of intestinal absorption of levothyroxine is only partially understood. Although phenytoin and other enzyme inducers can increase the elimination of thyroxine, the available data do not suggest that levothyroxine is a substrate for any major drug metabolizing CYP-enzyme. However, the absorption of levothyroxine may involve transporters, such as OATP [14, 15].

Recently, we treated in our hospital a young 36 year old hypothyroid female patient, whose serum concentration of thyroxine had previously been within the therapeutic range during therapy with levothyroxine (100 μg day^{-1}). Her consumption of grapefruit juice had been marked, and her serum free thyroxine concentration (6.4 pmol l^{-1}) was now below the therapeutic range with TSH concentration (63.7 mU l^{-1}) being high, even after an increase in the levothyroxine dose to 150 μg day^{-1}. After the patient was recommended to drink less grapefruit juice, she attained a therapeutic serum free thyroxine concentration (17 pmol l^{-1}) and her TSH (0.291 mU l^{-1}) was observed to be in the normal range. The present study was conducted to investigate the possible influence of grapefruit juice on the absorption of levothyroxine in healthy subjects.

Methods

Subjects

Ten healthy subjects (eight men and two women; age range 20–30 years; body mass index range 19.0–24.9 kg m^{-2}) participated in the study. Each subject was ascertained to be in good health as assessed by a medical history, clinical examination, and routine laboratory testing, and all had normal thyroid function. Only subjects with serum concentrations of TSH and free thyroxine within the normal ranges were recruited. Female participants were required to have a negative pregnancy test result. No subjects were taking any continuous medication (e.g. oral contraceptives), and all were nonsmokers. The consumption of grapefruit and orange juice was not allowed for 1 week before the first study day. The protocol was approved by the Ethics Committee for Studies in Healthy Subjects of the Hospital District of Helsinki and Uusimaa and by the National Agency for Medicines. The subjects gave their written informed consent before entering the study.

Study design

A randomized crossover design with two phases was used with an interval of 4 weeks. Subjects ingested 200 ml normal-strength grapefruit juice (Valio; Valio Ltd, Helsinki, Finland) or water (200 ml) three times a day (at 07.00 h, 12.00 h, and 20.00 h) for 2 days. On day 3, each subject ingested 600 μg levothyroxine (six Thyroxin 100 μg tablets; Yamanouchi, Japan) with 200 ml grapefruit juice or water at 09.00 h. In addition, the subjects received 200 ml grapefruit juice or water at 08.00 h and 10.00 h on day 3. Subjects fasted overnight before the administration of levothyroxine. Four hours after the levothyroxine dose, they were given a hot meal. Subjects were not allowed to drink coffee, tea or cola during the study.

Sampling

Two timed blood samples for the determination of serum T4 were drawn from a forearm vein within 90 min before administration of levothyroxine and at 0.5, 1, 1.5, 2, 3, 4, 6, and 24 h later. TSH concentrations were measured twice at baseline and once at 24 h. Serum was separated and stored at −70 °C until analyzed.

Hormone assays

Serum total thyroxine (T4) concentrations of the 10 healthy subjects following ingestion of 600 μg levothyroxine were measured by a luminoimmune assay (Vitros ECi, Ortho Clinical Diagnostics, USA). The method was linear over the range 4–300 nmol l^{-1} (normal values 71–141 nmol l^{-1}). The intra-assay coefficient of variation (CV) was 0.9% and the interassay CV was 5.1%. Serum concentrations of thyroid-stimulating hormone (TSH) were measured by a Chemiluminescence Microparticle Immunoassay (Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). The limit of determination of the method was 0.005 mU l^{-1} (normal range of 0.2–4.0 mIU l^{-1}). TSH was measured before ingestion of levothyroxine and 24 h later.

Pharmacokinetic analysis

The baseline concentrations of total T4 and TSH were calculated as the mean of two separate predose measurements. The increase in serum concentrations of total T4 was calculated by subtracting the baseline concentration from that measured at each time point. From these data the maximal increase in serum total T4 (dC_{max}) and time to dC_{max} (t_{max}) were derived directly. The incremental areas under the serum T4 *vs.* time curve (the area above baseline) from 0 to 4 h [dAUC(0,4 h)] and from 0 to 6 h [dAUC(0,6 h)] were calculated using the trapezoidal rule. After oral ingestion, levothyroxine is distributed primarily into the splanchnic and vascular space during the first 6 h, and the increase in serum T4 is proportional to the total amount of absorbed levothyroxine for this period. The amount of absorbed levothyroxine was esti-

mated by multiplying the maximal increase in T4 concentration by the volume of distribution (V_d) which was calculated from the body mass index (BMI) [16]:

$$V_d = 0.442 \times \text{BMI}$$

The incremental area under the serum T4 concentration-time curve from zero to t h [dAUC(0,t)] was, calculated using the trapezoidal rule.

Statistical analysis

The maximal increase in serum total T4 (dC_{max}), the increase in serum T4 concentration at 24 h, the dAUC(0-t) of T4, the amount of levothyroxine absorbed, and the decrease in serum TSH concentration after ingestion of levothyroxine were analyzed by the paired Student's t-test (two-tailed). In addition, 95% confidence intervals (CI) were calculated on the mean differences between phases. The nonparametric Wilcoxon rank-sum test was used for analysis of t_{max}. The statistical program Systat for Windows, version 6.0.1 (Systat, Evanston, IL, USA) was used.

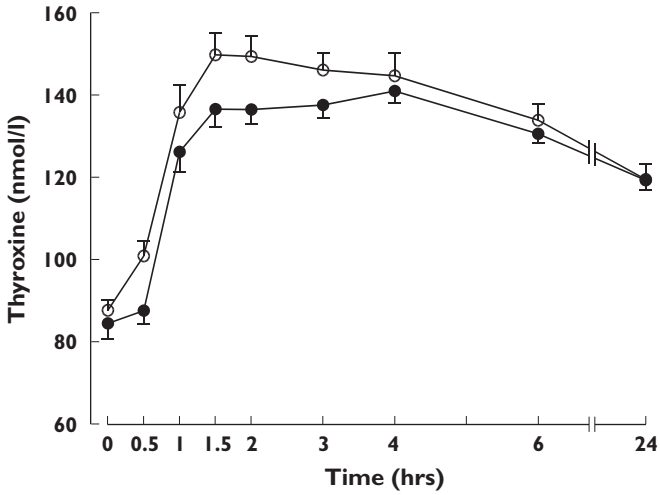

Figure 1
Effect of grapefruit juice (200 ml) (●) or water (○) taken three times a day for 3 days on the mean (± SEM) unadjusted serum concentrations of thyroxine in 10 healthy subjects after a single oral dose of 600 μg levothyroxine. On day 3, grapefruit juice (200 ml) or water was ingested 1 h before, at the same time as, and 1 h after levothyroxine administration

Results

During the control phase, serum concentrations of total T4 started to increase within 30 min after administration of levothyroxine 600 μg (Figure 1). Grapefruit juice decreased the mean dC_{max} by 11% (range, –22% to 7%) ($P < 0.01$), the mean dAUC(0,4 h) by 13% ($P < 0.05$) and the mean dAUC(0,6 h) by 9% ($P = 0.085$) (Table 1). During the control phase, the mean amount of levothyroxine absorbed was 85% of the ingested dose and the median t_{max} was 1.75 h (Table 1). After ingestion of grapefruit juice, the mean amount of levothyroxine absorbed was 76% of the dose and the median t_{max} 3 h. Serum concentrations of T4 decreased subsequently between 6 and 24 h. The decline in the serum concentration of TSH measured 24 h after levothyroxine ingestion was not altered by grapefruit juice (Table 1).

Discussion

In the present study, grapefruit juice showed limited effects on the pharmacokinetics of levothyroxine, the amount absorbed was only slightly decreased, and the t_{max} was not significantly prolonged.

Measurement of T4 was performed by a nonisotopic method, a limitation of which is that the exogenously ingested hormone cannot be distinguished from the endogenous hormone. Accordingly, the pharmacokinetic parameters for levothyroxine were calculated from its serum concentrations up to 6 h only. Ingestion of levothyroxine decreases the synthesis of endogenous T4, which has a long elimination half-life of about 6–7 days. Thus, the feedback inhibition of T4 synthesis by exogenous levothyroxine will not affect significantly (less than 4%) the plasma concentration of T4. A relatively high dose of 600 μg of levothyroxine was used to increase markedly serum thyroxine concentrations which allowed for a reliable estimation of the dAUC(0,6 h) of thyroxine. The power of our study was sufficient to detect a possible clinically important change in levothyroxine absorption. Furthermore, a large quantity of grapefruit juice was ingested to maximize the ability to detect an interaction.

Previous pharmacokinetic studies suggest that levothyroxine is not subject to extensive first-pass metabolism by CYP enzymes, because its oral bioavailability in fasting subjects is about 70–80%. Levothyroxine is susceptible to complexation with other drugs in the gastrointestinal tract [10, 11], and grapefruit juice is characterized by its acidity [7]. Thus, grapefruit juice components appear to have only a minor potential to interfere with the absorption of levothyroxine from the intestinal lumen either by binding to the drug or by increasing the acidity of the gastrointestinal tract.

Recently, it has been shown that grapefruit juice markedly decreases plasma concentrations of fexofenadine and celiprolol [6, 7]. It has been suggested that the mechanism of the grapefruit juice–fexofenadine interaction is inhibition of uptake transporters in the intestinal wall that results in decreased absorption [6]. Little

Table 1
Pharmacokinetics of a single 600 μg dose of levothyroxine in 10 subjects after co-administration with water or grapefruit juice

Variable	Water phase	Grapefruit juice phase	Mean difference (95% CI) between phases
T4 at baseline (nmol l^{-1})	87.7 ± 7.8	84.5 ± 11.9	–3.2 (–13.8, 7.4)
dC_{max} (nmol l^{-1})	66.4 ± 10.5	59.4 ± 7.4**	–7.0 (–11.3, –2.7)
Percentage of control (range)	100%	89% (78–107%)	
t_{max} (h)	1.75 (1.5–4)	3 (1–4)	0.8 (–0.4, 1.9)
dAUC(0,4 h) (nmol l^{-1} h)	195 ± 42.1	169 ± 31.2*	–26 (–51, –1)
Percentage of control (range)	100%	87% (62–134%)	
dAUC(0,6 h) (nmol l^{-1} h)	298 ± 58.6	271 ± 43.2†	–27 (–58, 4)
Percentage of control (range)	100%	91% (76–128%)	
Levothyroxine absorbed (μg)	511 ± 87.7	457 ± 59.9**	–54 (–90, –19)
Percentage of dose (range)	85% (58–110%)	76% (56–91%)	
TSH (mU l^{-1}) before levothyroxine	1.79 ± 0.94	1.86 ± 0.95	0.07 (–0.29, 0.42)
dTSH (mU l^{-1}) after levothyroxine	1.25 ± 0.72	1.22 ± 0.72	–0.03 (–0.33, 0.26)

*Data are mean values (± SD); t_{max} values are given as median with ranges. dC_{max}, maximal increase in serum concentration of thyroxine (T4); t_{max}, time to reach dC_{max}; dAUC(0,t), incremental area under the serum concentration-time curve from zero to t h; levothyroxine absorbed is calculated by multiplying the dC_{max} of T4 by the estimated volume of distribution of levothyroxine; TSH, thyroid-stimulating hormone; dTSH, serum TSH at 24 h minus the baseline TSH (at time 0). **P < 0.01 vs. water phase (control), *P < 0.05 vs. water phase, †P = 0.085 vs. water phase.*

is known about the mechanism of the absorption of levothyroxine. Thyroxine is poorly soluble in water, and its uptake, at least in some organs, for example brain, appears to depend on transporters. Of those involved in the disposition of levothyroxine, OATP-A and OATP-E have been reported to be expressed in the intestinal wall [14, 15]. The results of the present study suggest that grapefruit juice does not interfere with the action of these transporters. However, it cannot be excluded that the longterm use of grapefruit juice might interfere with the enterohepatic recycling of levothyroxine, because the present study was designed to investigate the absorption, not the elimination, of levothyroxine. Furthermore, it can be speculated that in some individuals (as in our index patient) certain transporters could be particularly important in the intestinal absorption of levothyroxine, and thus inhibition by grapefruit juice could cause a substantial decrease in the bioavailability of levothyroxine.

In conclusion, repeated consumption of grapefruit juice had a minor effect on the absorption of levothyroxine in healthy subjects. A clinically relevant interaction between grapefruit juice and levothyroxine appears unlikely.

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