Grapefruit Juice Increases Serum Concentration of Carbamazepine in Epileptic Children

Wpływ soku grejpfrutowego na stężenie karbamazepiny w surowicy krwi u dzieci z padaczką

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STRESZCZENIE

Wstęp. Dane z piśmiennictwa wskazują, że jednoczasowe podawanie soku grejpfrutowego (SG) z niektórymi lekami, w tym z lekami przeciwpadaczkowymi, zwiększa ich stężenie w surowicy krwi. Liczne badania potwierdziły, że flawonoidy zawarte w SG są inhibitorami enzymów cytochromu P-450, biorących udział w metabolizmie leków. Karbamazepina (CBZ), powszechnie stosowany lek przeciwpadaczkowy, jest metabolizowana w wątrobie w cyklu enzymatycznym cytochromu P-450. Doniesienia dotyczące wpływu SG na metabolizm CBZ są niezwykle skąpe, co skłoniło nas do przeprowadzenia obecnego badania. W grupie pacjentów z padaczką leczonych w monoterapii CBZ ocenialiśmy wpływ SG na stężenie CBZ w ich surowicy krwi po 5 i 10 dniach jednoczesnego przyjmowania soku. **Pacjenci i metodyka.** W badaniu uczestniczyło 15 dzieci (9 chłopców i 5 dziewcząt) w wieku 8–16 lat (średnio 12,2 ± 2,59 roku życia) z padaczką z napadami częściowymi złożonymi. Wszyscy pacjenci byli leczeni stabilną dawką CBZ (Tegretol CR) podawaną 2 razy dziennie. Średnia dobowa dawka leku wynosiła 17,06 ± 4,6 mg/kg. Trzydzieści minut przed każdą dawką CBZ pacjenci wypijali 250 ml SG. Stężenie CBZ w surowicy oceniano metodą polaryzacyjno-immunofluorescencyjną analizatorem TDx Abbott. Do analizy statystycznej użyto testu ANOVA. **Wyniki i wnioski.** Wykazaliśmy, że SG zwiększa stężenie CBZ w surowicy krwi dzieci z padaczką. Wzrost stężenia CBZ nie był znamienny statystycznie. Interakcja farmakologiczna pomiędzy SG i CBZ powinna być brana pod uwagę w praktyce klinicznej w celu uniknięcia zależnych od stężenia potencjalnych działań niepożądanych leku.

Słowa kluczowe: sok grejpfrutowy, karbamazepina, dzieci, padaczka

ABSTRACT

Introduction. It has been found that the flavonoids of grapefruit juice inhibit the drug-metabolizing enzymes of the cytochrome P-450 system. Carbamazepine (CBZ) undergoes extensive hepatic metabolism through the cytochrome P-450 enzyme system. It exhibits autoinduction, increasing the rate of its own elimination when dosing is initiated or modified. Current studies have demonstrated that concurrent administration of grapefruit juice increases plasma concentrations of several drugs, including antiepileptics. In the present study, we determined the effect of grapefruit juice intake on CBZ serum concentration after 5 and 10 days of its administration in epileptic children. **Subjects and methods.** Fifteen children (9 boys and 6 girls) aged from 8 to 16 years (mean 12.2 ± 2.59 years) with complex partial seizures participated in this study. All patients were treated with a stable dose of CBZ (Tegretol CR) monotherapy, given twice daily. The mean dose of CBZ was 17.06 ± 4.6 mg/kg/day. The patients took 250 mL of grapefruit juice 30 minutes before each administration of Tegretol CR. CBZ concentration in serum was determined by immunofluorescence polarization method using TDx Abbott analyzer. **Results.** We found an increase in CBZ serum concentration after intake of grapefruit juice compared with day 0, although this increase was not statistically significant. **Conclusion.** Co-administration of grapefruit juice with CBZ resulted in a mild increase of serum CBZ concentration in epileptic children. Interaction between grapefruit juice and CBZ should be taken into account by clinicians in chronic therapy of epilepsy to avoid potential concentration-dependent adverse effects of CBZ.

Key words: grapefruit juice, carbamazepine, children, epilepsy

INTRODUCTION

Several previous studies have demonstrated that concurrent administration of grapefruit juice increases plasma concentrations of several drugs [1–3]. It was found that the flavonoids in grapefruit juice inhibit the drug-metabolizing enzymes of the cytochrome P-450 system [3].

Cytochrome P450-3A4 has a broad substrate specificity and biotransforms many drugs, including: dihydropyridine calcium channel blockers, lidocaine, astemizole, terfenadine, cyclosporine, and short-acting benzodiazepines such as midazolam and triazolam. This could result in significant interactions between drugs, especially with those which inhibit cytochrome P450-3A4, i.e, macrolide antibiotics [4]. Naringenin, quercetin, and kaempferol are flavonoids present as glycosides in grapefruit juice and have demonstrated inhibition of in vitro metabolism of dihydropyridine calcium channel antagonists, felodipine and nifedipine [1].

The degree of inhibition was related to the chemical structures and concentrations of the flavonoids. Naringin, the glycoside of naringenin, is the major flavonoid found in

grapefruit juice. However, naringin has no apparent effect on human cytochrome P-450 enzymes. Naringin is apparently hydrolyzed in the intestine to naringenin and naringenin glucuronides [5]. In contrast to naringin, naringenin is a potent inhibitor of several enzyme families, including CYP3A4, CYP1A2, and 11beta-hydroxysteroid dehydrogenase [1,6].

Edwards et al. demonstrated that grapefruit oil and two furanocoumarin constituents (6', 7'-dihydroxybergamottin and a closely related dimer) caused a dose-dependent fall in CYP3A4 catalytic activity and immunoreactive CYP3A4 concentration [7]. Schmiedlin-Ren et al. [8] showed that the reduction in intestinal CYP3A4 concentration is rapid; a 47% decrease occurred in a healthy volunteer within 4 hrs. after consuming grapefruit juice. Another potent furanocoumarin is bergamottin. It was found that bergamottin inactivated P450 3A4, NADPH-cytochrome P450 reductase, cytochrome b5, and phospholipids. Bergamottin was also found to inhibit the activities of P450s 1A1, 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in human liver microsomes [9,10].

Carbamazepine (CBZ) is an antiepileptic drug, and it has become the drug of choice for the treatment of partial complex, and secondary generalized seizures [11–13]. In most patients, serum concentrations between 4 to 12 ug/mL result in seizure control without significant dose-related adverse effects. As with all anticonvulsants, clinicians should be aware of the highly patient-specific response to CBZ and tailor therapy to the individual [14]. CBZ undergoes extensive hepatic metabolism through the cytochrome P450 enzyme system. It exhibits autoinduction, increasing the rate of its own elimination when dosing is initiated or modified. In most patients, autoinduction plateaus after three to four weeks of therapy. In adults, the elimination half-life following a single dose ranges from 11 to 30 hours. With chronic dosing, half-life declines to approximately 5 to 14 hours. Similar values have been reported in children [15].

In the present study, we determined the effect of grapefruit juice on CBZ serum concentration after 5 and 10 days of its administration to epileptic children.

SUBJECTS AND METHODS

15 children (9 boys and 6 girls) aged from 8 to 16 years (mean 12.2 ± 2.59 years) with complex partial seizures participated in this study. All the patients underwent monotherapy with CBZ (Tegretol CR). The patients were maintained on a stable dose of their standard antiepileptic drug therapy for at least 30 days. Mean dose of CBZ was 17.06 ± 4.6 mg/kg/day. After fasting overnight, at 8 am and 6:30 pm the patients took 250 mL of grapefruit juice (Hortex-Poland) 30 minutes before intaking Tegretol CR (Novartis) tablets. At 7 pm, the children took Tegretol CR. Blood was drawn at 7.30 am before the intake of tablets at day 0, after 5 days' and 10 days' administration of grapefruit juice. Total serum CBZ concentration was measured by the standard polarized immunofluorescence method using TDx Abbott analyzer.

STATISTICS

The arithmetical means with the standard deviation of the values were calculated. Significant differences were verified by one-way ANOVA.

RESULTS

Details of the participating patients are summarized in Table I. The CBZ serum concentrations after the intake of grapefruit juice increased compared with day 0 (6.70 ± 1.23 ug/ml) (Fig.1). After 5 days' administration of the juice, the concentration of CBZ was 7.40 ± 1.21 ug/mL, but did not differ significantly ($F(3,11) = 0.7413$; $p = 0.5473$) compared to day 0. Similar results (7.90 ± 1.10 ug/mL) were obtained after 10 days' administration of grapefruit juice, and these concentrations did not differ significantly ($F(3,11) = 1.1658$; $p = 0.23290$ compared to day 0. We found a tendency for increased serum concentration of CBZ in our patients. In view of the small number of patients, we could not obtain significant differences in the CBZ concentration. Tolerance of the juice was good, no side-effects were reported during the study.

Table I. Characteristics of children with complex partial seizures

	Initials	Sex	Age (years)	Tegretol CR dose (mg/kg/day)
1	BM	m	13	15
2	KD	m	15	18
3	ZM	m	8	15
4	RH	m	14	10
5	JE	f	9	8
6	MM	m	15	20
7	BK	m	8	23
8	SK	m	16	25
9	SM	f	14	20
10	BZ	m	14	16
11	FT	f	10	15
12	KR	f	11	13
13	GT	m	13	20
14	ER	f	12	20
15	ML	f	11	18

CPS – complex partial seizures; f – female; m – male.

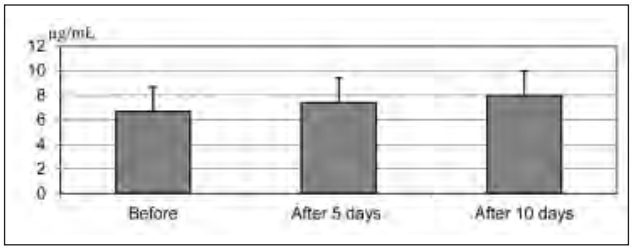

Figure 1. Plasma carbamazepine concentration (means ± SD) in epileptic children (n = 15) before, after 5 and 10 days of grapefruit juice administration .

DISCUSSION

Grapefruit juice is known to inhibit mammalian cytochrome P450 isozymes such as CYP3A4 [3]. Edwards et al. demonstrated that grapefruit oil and two furanocoumarin constituents (6', 7'-dihydroxybergamottin and a closely related dimer) caused a dose-dependent fall in CYP3A4 catalytic activity and immunoreactive CYP3A4 concentration [7]. Schmiedlin-Ren et al. [8] showed that the reduction in intestinal CYP3A4 concentration is rapid; a 47% decrease occurred in a healthy volunteer within 4 hrs. after consuming grapefruit juice. Another potent furanocoumarin is bergamottin. It was found that bergamottin inactivated P450 3A4, NADPH-cytochrome P450 reductase, cytochrome b5, and phospholipids. Bergamottin was also found to inhibit the activities of P450s 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in human liver microsomes [16].

Previous studies have found that grapefruit juice improved the bioavailability of benzodiazepines, cyclosporine and most calcium channel blockers [17–19]. It is important to notice that the whole fruit can cause the same effect as the juice [20].

Clinical reports focused on pharmacological interactions between grapefruit juice and carbamazepine are scarce. In the PubMed database, we found only one report prepared by Garg et al. [21]. The authors studied the effect of grapefruit juice on the bioavailability of CBZ in patients with epilepsy. Patients involved in the study received 200 mg of carbamazpeine 3 times a day. They were given either grapefruit juice or 300 mL of water with each CBZ dose. Compared with water, grapefruit juice significantly increased the steady peak concentration of CBZ, although no significant effect was found in the time to reach peak plasma concentration. In our study, we demonstrated that grapefruit juice increased serum concentration of CBZ in children with epilepsy. The mean concentration of CBZ increased from 6.68 up to 7.98 ug/mL after 10 days of juice intake. Our results are comparable to those obtained by Garg et al. [21], although the increase of CBZ serum concentration was not statistically significant. Recently, over-expression of multidrug transporters, such as P-glycoprotein (PGP) and multidrug resistance-associated protein 2 (MRP2), has been reported in surgically resected epileptogenic human brain tissue and suggested to contribute to the drug resistance of epilepsy. The aim of an experimental study performed by Potschka et al. [22] was to assess whether the concentration of CBZ in the extracellular fluid of the rat's cerebral cortex can be enhanced by inhibition of PGP or MRP. Authors used the PGP inhibitor verapamil and the MRP inhibitor probenecid. Local perfusion with verapamil or probenecid via the microdialysis probe increased the extracellular concentration of CBZ. These data indicated that both PGP and MRP participated in the regulation of extracellular brain concentrations of CBZ. Grapefruit products have also been associated with interactions with PGP and uptake transporters, e.g. organic anion-transporting polypeptides. Polyphenolic compounds such as grapefruit flavonoids have been proposed as the causative agents of the PGP interactions [3,23].

Summing up, grapefruit juice increases the bioavailability and concentration of CBZ in serum by inhibiting CYP3A4 enzymes in the intestine wall, the liver, and probably by other mechanisms. From the clinical practice perspective, grapefruit juice should not be used by CBZ-treated epileptic patients to avoid unfavorable fluctuations of CBZ concentration, which may result in the presence of concentration-dependent adverse effects of CBZ.

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