Effects of liquid and freeze-dried grapefruit juice on the pharmacokinetics of praziquantel and its metabolite 4′-hydroxy praziquantel in beagle dogs

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Abstract

Grapefruit juice changes the pharmacokinetic parameters of a variety of drugs metabolized primarily by cytochrome P450 3A. In a three-phase crossover study, six male beagle dogs were administered 100 ml of water (control), 100 ml of commercial liquid grapefruit juice, or 10 g of freeze-dried grapefruit juice (equivalent to 100 ml of liquid grapefruit juice) with 100 ml of water, followed after 2 h by single oral dose of praziquantel ($30\,\mathrm{mg\,kg^{-1}}$). After treatment, the dogs were sampled at different times. Determination of praziquantel and its metabolite 4′-hydroxy praziquantel (identified by GC/MS) was performed by HPLC. Liquid and freeze-dried grapefruit juice preadministration increased the C_{max} of praziquantel about three-fold and the AUC 2.5- and 2.3-fold, respectively. The T_{max} (0.75 h) was unaffected by liquid or freeze-dried grapefruit juice, while $T_{1/2}$ was 2.3- and 1.7-fold higher compared with controls. The amount of 4′-hydroxy praziquantel was also affected by both liquid and freeze-dried grapefruit juice administration: the AUC and C_{max} increased four- and three-fold, respectively and the T_{max} was significantly enhanced.

These findings demonstrate that both freeze-dried grapefruit juice and commercial liquid grapefruit juice significantly increase plasma concentrations and $T_{1/2}$ of praziquantel in dogs.

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1. Introduction

Grapefruit juice (L-GFJ) modifies the pharmacokinetic parameters of a variety of drugs, including dihydropyridine calcium channel blockers, cyclosporine, tacrolimus, midazolam, triazolam, terfenadine, diazepam, carbamazepine, saquinavir, ethynylestradiol and caffeine [1]. Since these drugs are metabolized primarily by cytochrome P450 3A (P450 3A), it has been suggested that the effects of L-GFJ may be due to the inhibition of P450 3A enzymes [2–4]. The mechanism of this decrease in P450 3A protein probably reflects either an accelerated protein degradation or a reduced messenger RNA translation [5]. The effects can be particularly important for orally administered drugs, because P450 3A is located not only in hepatocytes, but also in the epithelial cells of the intestine. In this latter tissue, P450 3A is the most frequently expressed P450 enzyme, and is responsible for the first pass-effect metabolism.

Several points indicate that a single dose of L-GFJ (200 ml) acts on the P450 system at the intestinal, but not at the hepatic level: (i) the medications that interact with L-GFJ undergo metabolism by P450 3A enzymes in the small bowel; (ii) L-GFJ increases the area under the plasma concentration–time curve (AUC), probably the best measurement of the body's exposure to a drug, with minimal changes in the clearance or half-life; (iii) L-GFJ has no effect on the pharmacokinetics of these medications when they are given intravenously [6–9]. On the other hand, multiple daily ingestion of L-GFJ for a few days may lead to the inhibition of hepatic P450 3A [10,11]. Many compounds have been proposed to be the active ingredients in L-GFJ, these include both flavonoids and furanocumarins [12]. However, the active components responsible for in vivo inhibition of P450 3A activity, have yet to be fully determined [12,13].

Praziquantel, (PZQ, 2-cyclohexylcarbonyl [1,2,3,6,7,11b] hexahydro-4H-pyrazin [2,1a] isoquinolin-4-one), is a broadly effective trematocide and cestocide [14], widely used in both veterinary [15] and human medicine [16,17]. Following oral administration, PZQ is rapidly absorbed, followed by a fast and extensive first pass-effect metabolism

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[18–20]. PZQ possesses a wide therapeutic index, and its adverse effects are evident only after very high doses [21]. The oral bioavailability of PZQ changes among animal species but it is usually quite low [18,20]. It has also been observed that its metabolism is probably mediated by P450 3A both in animals and in humans [20,22–25]. Moreover, early study shows that in humans L-GFJ administered with PZQ significantly increased both AUC and C_{max} of the drug [26].

The aim of the present study was to investigate the effects of a single dose (100 ml) of L-GFJ and freeze-dried GFJ (FD-GFJ) on the pharmacokinetics of PZQ and its major metabolite 4′-hydroxy praziquantel (4′OH-PZQ) in healthy beagle dogs.

2. Materials and methods

2.1. Chemicals

Pure PZQ and 4′OH-PZQ, and epsiprantel were kindly supplied by Merck (Darmstadt, Germany) and Pfizer (Rome, Italy), respectively (Fig. 1). L-GFJ (sugar-free) was from Santal (Parmalat, Parma, Italy); the same batch number was used throughout the study, to avoid the disparities in the various components of this fruit juice such as flavonoids which could be season dependent. All the other chemicals and solvents of analytical or super gradient grade were supplied from commercial sources.

2.2. Animal treatment and blood collection

The study was performed using six male beagle dogs, 2 years old, weighing 12–15 kg. The animals were individually caged in temperature-controlled rooms with a 12 h light cycle at 20–22 °C and 50–60% relative humidity. They were fed standard laboratory chow and tap water ad libitum. Their care and handling were in accordance with the indications of the European Economic Community (EEC) Council Directive 86-609, recognized and adopted by the

Italian Government (DL 27/01/1992, No. 116). The dogs were clinically healthy, as determined by a complete physical examination and routine haematological and clinical chemistry analyses. To facilitate blood collection, under light anesthesia, a dwelling catheter was inserted into the external jugular vein of all animals 2 days before the treatment, and it was washed daily with 2 ml of heparin (5000 IU l^{-1}). They received any food for 24 h before and after treatment. The dogs were administered 100 ml of water followed after 2 h by an oral single dose of Neomansonil® (PZQ 30 mg kg^{-1}, Bayer, Kiel, Germany). After treatment, the animals were sampled at 0.08, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 24 h. Blood samples were stored at −20 °C. After a period of 7 days (washout), the dogs received 100 ml of L-GFJ and an oral single dose of PZQ (30 mg kg^{-1}) 2 h later and, after treatment, blood collection was performed again at the same times. After another 7 days washout period, animals were administered a dose of 10 g of FD-GFJ (equivalent to 100 ml of L-GFJ) with 100 ml of water followed after 2 h by an oral single dose of PZQ (30 mg kg^{-1}); blood collection was performed again at the same times.

2.3. HPLC analysis

Plasma extraction and HPLC analysis of PZQ and 4′OH-PZQ concentrations were performed in accordance with the method of Xiao et al. [27], partially modified [20], using a Waters Spherisorb C18 ODS2, 5 μm, (25 cm × 4.6 mm) column, with a Waters Guard Pack insert resolve C18 (Waters, Milford, MA, USA) precolumn, as the stationary phase. Epsiprantel (5 μg ml^{-1}) was used as internal standard (recovery 90 ± 6%). The precision of the method was expressed as the coefficient of variation (CV) of the results obtained from different analyses (CV < 8%). The accuracy of the method was defined as the difference between the actual and theoretical values, expressed according to mean percentage error (ME < 15%). The linearity of the method was assayed between 50 and 5000 ng ml^{-1}. The PZQ and 4′OH-PZQ peak areas relative to the internal standard were calculated and plotted versus the concentrations. The concentrations of PZQ and 4′OH-PZQ in plasma samples were calculated from calibration curves previously constructed. The limit of quantization of the methods was 50 ng ml^{-1}. Each test was performed in duplicate at room temperature (24 °C).

2.4. GC/MS analysis

The detection of the unknown peak was performed by GC/MS with a Fison 8000 GC and a Fison MD 800 MS (Milan, Italy). It was isolated on a Mega® OV-1 fused-silica capillary column (15 m × 0.18 mm i.d., 0.1-mm film thickness; Fison, Milan, Italy). The injector was operated in the splitless mode at 250 °C, and helium was used as the carrier gas at a column head pressure of approximately 6 psi and a flow rate of 1 ml min^{-1}. Specimens ($\cong$1 μl) were injected at
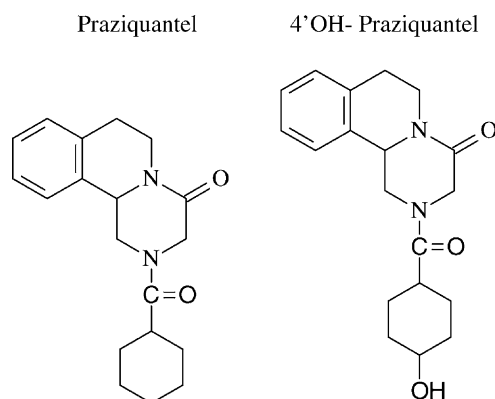

Praziquantel   4'OH- Praziquantel

Fig. 1. Molecular structures of PZQ and its main metabolite 4′OH-PZQ.

100 °C; the split valve was opened after 1 min and the temperature was increased to 295 °C at a rate of 15 °C min^{-1}. When it reached 295 °C, the course was extended for 10 min. The ion source was operated at 180 °C with an accelerating voltage of 70 eV, 750 mA filament current and 1 kV electron multiplier voltage (the conversion dynodes operated at 5 kV).

2.5. FD-GFJ and its reconstitution

One hundred milliliter of commercial L-GFJ was divided into two equal portions in plastic tubes, frozen in liquid N$_2$ and freeze-dried using Edwards equipment (Edwards, Milan, Italy). At the end of the process, the residue was collected, weighed (10 g) and compressed in a manual compressor (Carlo Erba, Milan, Italy) giving five tablets (2 g each).

The reconstitution was carried out with water (100 ml) at 39 °C in a Stuart Scientific water bath with constant shaking (30 cycles min^{-1}). The time for the dissolution of the five tablets was 40 min.

2.6. Pharmacokinetic analysis

When the plasma concentration–time curves of PZQ from individual dogs administered the three different treatments were analyzed using the Easy Fit program (Mario Negri Institute, Milan, Italy), the results were consistent with a linear one-compartment open model with a correlation coefficient (r) >0.96. The maximum concentration (C_{max}) and time to maximum (T_{max}) were obtained directly from the data. The area under the serum curve up to the last quantified data point [AUC (0–10)] was calculated by the trapezoidal rule and the AUC (0–∞) with extrapolation to infinity. The half-life of plasma concentrations ($T_{1/2}$) was calculated as $0.693/\beta$.

2.7. Statistical analysis

The data were expressed as means ± standard error (S.E.). Data were analyzed by the Student's t-test. Differences were regarded as statistically significant at $P < 0.05$.

3. Results

The therapeutic dose of PZQ in the dog is 3.75 mg kg^{-1}, but in the present study animals were administered 30 mg kg^{-1} PZQ to obtain a clear plasma detection of the drug as reported in previous pharmacokinetic studies [20,24]. L-GFJ and FD-GFJ preadministration increased the PZQ extent of absorption, with an about three-fold increase in the C_{max} (Fig. 2). L-GFJ and FD-GFJ increased the AUC 2.5- and 2.3-fold, respectively. The T_{max} (0.75 h) was unaffected by L-GFJ or FD-GFJ, while the elimination phases were longer compared with control values (the half-life increased 2.3 times for L-GFJ and 1.7 times for FD-GFJ). The pharmacokinetic parameters are reported in Table 1A. Significant differences between L-GFJ and FD-GFJ pretreatment are not observed. As a time-increasing peak (retention time 5.60 min) appeared in the HPLC chromatogram, some samples were analyzed with a GC/MS apparatus. From the analysis of the mass spectrum the unknown peak proved to be that of 4'OH-PZQ. A new calibration curve was constructed using pure standard 4'OH-PZQ and a quantitative analysis of its concentration versus time in dog plasma was performed. L-GFJ and FD-GFJ preadministration increased the AUC and C_{max} of 4'OH-PZQ about four- and three-fold, respectively, while the $T_{1/2}$ was unaffected (Fig. 3). The T_{max} was also significantly enhanced by 25% (Table 1B).
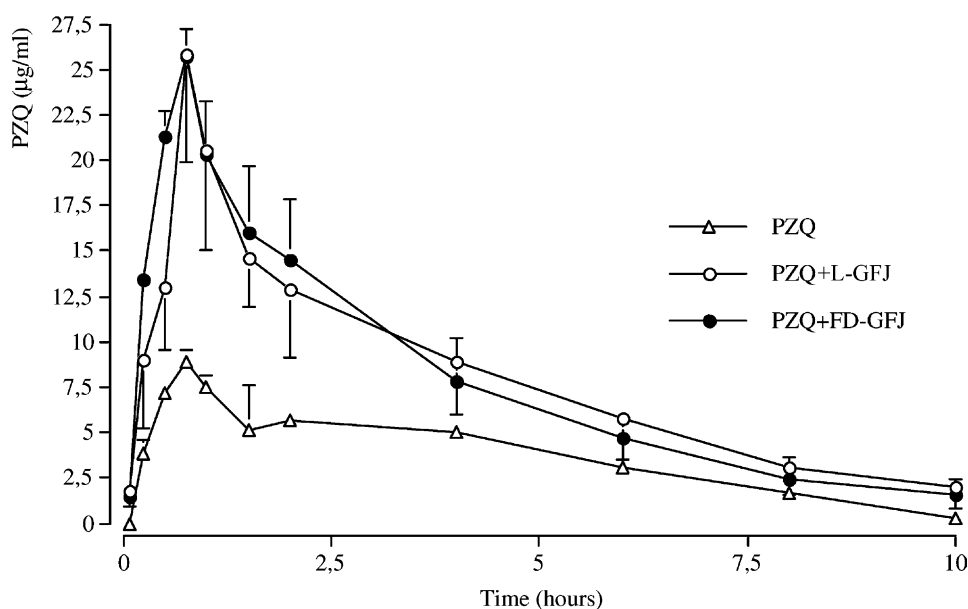

Fig. 2. Plasma concentration–time curves of PZQ after a single oral dose of PZQ (30 mg kg^{-1}, △), PZQ + L-GFJ (○) or PZQ + FD-GFJ (●).

Table 1
Pharmacokinetic parameters of PZQ (A) and 4′OH-PZQ (B) (means ± S.E.) after treatment of dogs with 100 ml of water (PZQ), with 100 ml of liquid GFJ (PZQ + L-GFJ), or with 10 g of freeze-dried (PZQ + FD-GFJ) with 100 ml of water, followed after 2 h by a single oral dose of PZQ (30 mg kg^{-1})

Parameters	PZQ	PZQ + L-GFJ	PZQ + FD-GFJ
A			
AUC (μg h ml^{-1})	42.3 ± 7.8	89.6 ± 30.7*	83.8 ± 14.5**
C_{max} (μg ml^{-1})	8.9 ± 0.7	25.9 ± 5.9**	25.7 ± 1.5**
T_{max} (h)	0.75	0.75	0.75
$T_{1/2}$ (h)	1.3 ± 0.3	2.73 ± 0.64**	2.18 ± 0.3*
B			
AUC (μg h ml^{-1})	32.08 ± 2.9	142.3 ± 12.75**	132.71 ± 17.46**
C_{max} (μg ml^{-1})	7.82 ± 0.49	22.08 ± 2.11**	20.75 ± 2.63**
T_{max} (h)	1.58 ± 0.08	2*	2*
$T_{1/2}$ (h)	1.92 ± 0.25	2.38 ± 0.24	2.14 ± 0.18

C_{max}: peak plasma concentration; T_{max}: time of peak plasma concentration; $T_{1/2}$: half-life; AUC: area under the plasma concentration–time curve.
 * Significantly different from PZQ (control) administration by Student's *t*-test $P < 0.05$.
 ** Significantly different from PZQ (control) administration by Student's *t*-test $P < 0.01$.
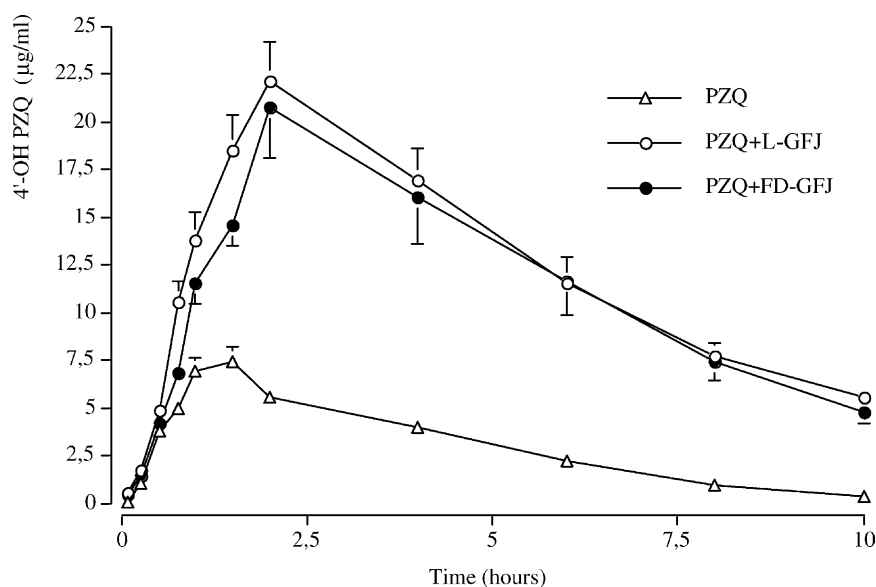

Fig. 3. Plasma concentration–time curves of 4′OH-PZQ after a single oral dose of PZQ (30 mg kg^{-1}, △), PZQ + L-GFJ (○) or PZQ + FD-GFJ (●).

4. Discussion

Almost 10 years ago some investigators observed an interaction between felodipine and L-GFJ [28,29]; some years later it was demonstrated that this interaction is due to the inhibition of the intestinal P450 3A [5], which is responsible for the biotransformation of fairly lipophilic substrates with a high molecular weight [30]. When cyclosporine/L-GFJ coadministration was tested [31,32], it was hypothesized that, due to the high cost of the drug, this association could be used to increase cyclosporine bioavailability and to obtain a substantial cost saving for patients [33]. Therefore L-GFJ was proposed as both a "natural" and a safe means of cost reduction for patients taking cyclosporine and as a coformulant for oral pharmaceutical preparations [34,35]. In the last few years, initial euphoria and assumptions have been substituted by suitable studies and careful evaluations, and it has been reported that many drug/L-GFJ coadministrations should be avoided because elevated plasma concentrations of drugs can evoke adverse effects. Side-effects due to the high levels of drugs have been demonstrated for cisapride, diazepam, midazolam, triazolam, buspirone and felodipine [1]. Moreover no pharmaceutical preparation containing L-GFJ and drugs has been proposed, because the acidic grapefruit juice pH could be responsible for an accelerated degradation of the drug in the pharmaceutical preparation (a short drug expiry time is in contrast with the objective of the pharmaceutical companies), though recent studies suggest that also neutralized GFJ could increase the drug bioavailability [36]. L-GFJ has been coadministered with drugs only if the patient is daily monitored, as reported for cyclosporine hospital administration.

In the present study beagle dogs were used, by assuming that some conclusions derived from humans could be

also applicable also to dogs. L-GFJ more than doubled the mean AUC and almost tripled the mean C_{max} of a single PZQ oral dose, suggesting an increased bioavailability of the drug. The magnitude of the interaction was variable among dogs, but the AUC and C_{max} obtained with L-GFJ were reproducible within animals. Thus, as also reported in humans [37], determinant(s) of the L-GFJ interaction appear to be mainly inherent in the single animal. The marked increase in the PZQ C_{max} after L-GFJ administration, with no change in the T_{max}, suggests that, also in dogs, the effects of L-GFJ influence the absorption phase of the drug, as previously reported in humans [38].

These findings suggest that the intestinal wall, where P450 3A is extensively expressed, is one of the most important sites of L-GFJ and PZQ interaction. Although the significant increase in $T_{1/2}$ after L-GFJ and FD-GFJ is in contrast with previous results [5], where L-GFJ selectively down-regulates P450 3A in the small intestine without any effect on liver P450 3A, the present results are in agreement with a recent study [39] showing that a single ingestion of liquid GFJ inhibits both intestinal and hepatic P450 3A enzymes. The increase in the $T_{1/2}$ could be explained by one of the following hypotheses: (i) inhibition of the intestinal P-glycoprotein transporter (Pgp) by L-GFJ and FD-GFJ, although previous data concerning the effects of GFJ on the Pgp are variable [5,40]. In the few last years it has been suggested that L-GFJ could cause a simultaneous irreversible inhibition of Pgp and P450 3A activity in the gut [41,42]; (ii) PZQ undergoes a high enterohepatic circulation [43], and a down-regulation of intestinal P450 3A by L-GFJ and FD-GFJ could contribute to the observed increase in the elimination $T_{1/2}$ values; (iii) the L-GFJ and FD-GFJ dose administered to dogs could be quite high and the down-regulation of P450 3A could affect both intestinal and hepatic enzymes [39].

The increase of PZQ AUC could be expected to produce a graded decrease in 4′OH-PZQ (major metabolite) AUC, but after L-GFJ and FD-GFJ preadministration an increase of AUC of about three-fold was observed. This increase, previously reported for felodipine/dehydrofelodipine [44], suggests that the effects of L-GFJ and FD-GFJ may not be limited to the inhibition of P450 3A, and that other P450 isozymes or enzymes could be involved, according to the inhibition of subsequent metabolic pathways (di- and tri-oxidation of PZQ) [45]. On the other hand, the unaffected $T_{1/2}$ of 4′OH-PZQ after L-GFJ and FD-GFJ preadministration may be due to the fact that 4′OH-PZQ does not undergo enterohepatic circulation.

In conclusion, this study shows that a single oral dose of five tablets of FD-GFJ has the same effect as 100 ml of commercial L-GFJ on the pharmacokinetics of PZQ in beagle dogs. By taking into account the high cost of PZQ, a new pharmaceutical preparation can be hypothesized; a tablet having PZQ inside and a covering of FD-GFJ, since the toxicity of PZQ due to high plasma levels is negligible [21]. This pharmaceutical preparation should be avoided in patients with neurocistocercosis coadministered carbamazepine and dexametasone [17], and in patients receiving other drugs with a narrow therapeutic index that are metabolized by P450 3A.

References

[1] Kane C, Lipsky J. Drug grapefruit juice interactions. Mayo Clin Proc 2000;75:933–42.

[2] He K, Iyer KR, Hayes RN, Sinz MW, Woolf TF, Hollenberg PF. Inactivation of cytochrome P450 3A4 by bergamottin, a component of grapefruit juice. Chem Res Toxicol 1998;11:252–9.

[3] Fukuda K, Ohta T, Ohshima Y, Ohashi N, Yoshikawa M, Yamazoe Y. Specific CYP3A4 inhibitors in grapefruit juice: furocumarin dimers as components of drug interaction. Pharmacogenetics 1997;7:391–6.

[4] Guo L-Q, Fukuda K, Ohta T, Yamazoe Y. Role of furanocumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. Drug Metab Dispos 2000;28:766–71.

[5] Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545–53.

[6] Kupferschmidt HHT, Ha HR, Ziegler WH, Meier PJ, Krahenbuhl S. Interaction between grapefruit juice and midazolam in human. Clin Pharmacol Ther 1995;58:20–8.

[7] Kupferschmidt HHT, Fattinger KE, Ha HR, Follath F, Krahenbuhl S. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998;45:355–9.

[8] Lundahl J, Regardh CG, Edgar B, Johnsson G. Effects of grapefruit juice ingestion-pharmacokinetics and haemodynamics of intravenously and orally administered felodipine in healthy men. Eur J Clin Pharmacol 1997;52:139–45.

[9] Rashid TJ, Martin U, Clarke H, Waller DG, Renwick AG, George CF. Factors affecting the absolute bioavailability of nifedipine. Br J Clin Pharmacol 1995;40:51–8.

[10] Rogers JD, Zhao J, Liu LD, Amin RD, Gagliano KD, Porras AG, et al. Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Clin Pharmacol Ther 1999;66:358–66.

[11] Veronese M, Burke J, Dorval E, Pequignot E, Waldman S, Greenberg H. Grapefruit juice (GFJ) inhibits hepatic and intestinal CYP3A4 dose-dependently. Clin Pharmacol Ther 2000;67:151 [Abstract PIII-37].

[12] Ho PC, Saville DJ. Inhibition of human CYP3A4 activity by grapefruit flavonoids, furanocoumarins and related compounds. J Pharm Pharm Sci 2001;4:217–27.

[13] Maskalyk J. Grapefruit juice: potential drug interactions. Can Med Assoc J 2002;167:279–80.

[14] Andrews P, Thomas H, Pohlke R, Seubert J. Praziquantel. Med Res Rev 1983;3:147–200.

[15] Morris DL, Richards KS, Clarkson MJ, Taylor DH. Comparison of albendazole and praziquantel therapy of *Echinococcus granulosus* in naturally infected sheep. Vet Parasitol 1990;36:83–90.

[16] Groll E. Praziquantel for cestode infections in man. Acta Trop 1980;37:293–6.

[17] Botero D, Castano S. Treatment of cysticercosis with praziquantel in Colombia. Am J Trop Med Hyg 1982;31:811–21.

[18] Steiner K, Garbe A, Diekmann HW, Nowak H. The fate of praziquantel in the organism I. Pharmacokinetics in animals. Eur J Drug Metab Pharmacokinet 1976;2:85–95.

[19] Groll E. Praziquantel. Adv Pharmacol Chemother 1984;20:219–38.

[20] Giorgi M, Salvatori AP, Soldani G, Giusiani M, Longo V, Gervasi PG, et al. Pharmacokinetics and microsomal oxidation of praziquantel and its effects on the P450 system in 3-month-old lambs infested by *Fasciola hepatica*. J Vet Pharmacol Ther 2001;24:251–9.

[21] Frohberg H. Results of toxicological studies on praziquantel. Arzneimittel-forsch 1984;34:1137–44.

[22] Vazquez ML, Jung H, Sotelo J. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. Neurology 1987;37:1561–2.

[23] Bittencourt PR, Gracia CM, Martins R, Fernandes AG, Diekmann HW, Jung W. Phenytoin and carbamazepine decreased oral bioavailability of praziquantel. Neurology 1992;42:492–6.

[24] Masimirembwa CM, Naik YS, Hasler JA. Effect of phenobarbital and 3-methylcholanthrene pre-treatment on the pharmacokinetics of praziquantel in rats. Eur J Drug Metab Pharmacokinet 1993;18:261–4.

[25] Masimirembwa CM, Hasler JA. Characterisation of praziquantel metabolism by rat liver microsomes using cytochrome P450 inhibitors. Biochem Pharmacol 1994;48:1779–83.

[26] Castro N, Jung H, Medina R, Gonzalez-Esquivel D, Lopez M, Sotelo J. Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 2002;46:1614–6.

[27] Xiao SH, Catto BA, Webster LT. Quantitative determination of praziquantel in serum by high-performance liquid chromatography. J Chromatogr 1983;275:127–32.

[28] Bailey DG, Spence JD, Munoz C, Arnold JMO. Interaction of citrus juices with felodipine and nifedipine. Lancet 1991;337:268–9.

[29] Edgar B, Bailey DG, Bergstrand R, Johnsson G, Regardh CG. Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine and its potential clinical relevance. Eur J Clin Pharmacol 1992;42:313–7.

[30] Oritz de Montellano PR, Reich NO. Inhibition of cytochrome P450 enzymes. In: Oritz de Montellano PR, editor. Cytochrome P-450. New York: Plenum; 1986, p. 273–314.

[31] Ioannides-Demos LL, Christophidis N, Ryan P, Angelis P, Liolios L, McLean AJ. Dosing implications of a clinical interaction between grapefruit juice and cyclosporine and metabolite concentrations in patients with autoimmune diseases. J Rheumatol 1997;24:49–54.

[32] Ku YM, Min DI, Flanigan M. Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? J Clin Pharmacol 1998;38:959–65.

[33] Keogh A, Spratt P, McCosker C, Macdonald P, Mundy J, Kaan A. Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. N Engl J Med 1995;333:628–33.

[34] Taniguchi S, Kobayashi H, Ishii M. Treatment of psoriasis by cyclosporine and grapefruit juice. Arch Dermatol 1996;132:1249.

[35] Emilia G, Longo G, Bertesi M, Gandini G, Ferrara L, Valenti C. Clinical interaction between grapefruit juice and cyclosporine: is there any interest for the hematologist? Blood 1998;91:362–3.

[36] Lee AJ, Chan WK, Harralson AF, Buffum J, Bui BC. The effects of grapefruit juice on sertraline metabolism: an in vitro and in vivo study. Clin Ther 1999;21:1890–9.

[37] Bailey DG, Arnold JMO, Bend JR, Tran LT, Spence JD. Grapefruit juice-felodipine interaction: reproducibility and characterization with the extended release drug formulation. Br J Clin Pharmacol 1995;40:135–40.

[38] Lundahl J, Regardh CG, Edgar B, Johnsson G. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. Eur J Clin Pharmacol 1995;49:61–7.

[39] Libersa CC, Brique SA, Motte KB, Caron JF, Guedon-Moreau LM, Humbert L, et al. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. Br J Clin Pharmacol 2000;49:373–8.

[40] Takanaga H, Ohnishi A, Matsuo H, Sawada Y. Inhibition of vinblastine efflux mediated by P-glycoprotein by grapefruit juice components in caco-2 cells. Biol Pharm Bull 1998;21:1062–6.

[41] Lilja JJ, Kivisto KT, Neuvonen PJ. Duration of effect on grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. Clin Pharmacol Ther 2000;68:384–90.

[42] Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. Life Sci 2002;71:1149–60.

[43] Diekmann HW, Buhring KU. The fate of praziquantel in the organism III. Metabolism in rat, beagle dog and rhesus monkey. Eur J Drug Metab Pharmacokinet 1976;2:107–11.

[44] Bailey DG, Malcolm AO, Munoz C, Spence JD. Grapefruit juice-felodipine interaction: mechanism, predictability and effect of naringin. Clin Pharmacol Ther 1993;53:637–42.

[45] Buhring KU, Diekmann HW, Muller H, Garbe A, Nowak H. Metabolism of praziquantel in man. Eur J Drug Metab Pharmacokinet 1978;3:179–90.