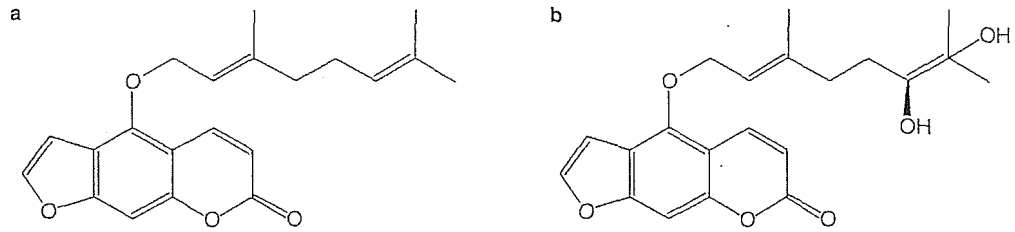

Fig. 3. Chemical structures of (a) bergamottin and (b) 6′,7′-dihydroxybergamottin.

furanocoumarins concentrated by centrifugation in the particulate fraction increased felodipine AUC 1.4 times more than the supernatant fraction in the above-mentioned clinical study.[117] Furthermore, Bailey et al.[12] reported that an extract of segment-free parts of grapefruit, which included more bergamottin and less 6′,7′-dihydroxybergamottin, increased felodipine AUC considerably more than the segments, again suggesting that bergamottin might be the major inhibitory component in grapefruit juice. However, diluted lime juice containing bergamottin in the same quantity as in grapefruit juice, but free from 6′,7′-dihydroxybergamottin, could only partially reproduce the effect of grapefruit juice on felodipine AUC and the investigators concluded that bergamottin was not a primary substance responsible for clinical inhibition of CYP3A4 activity.[10] Recently, however, findings from a study of furanocoumarin fractions of grapefruit diluted in orange juice supported the notion that 6′,7′-dihydroxybergamottin contributes to the grapefruit juice-felodipine interaction.[118]

Bergapten is another ingredient found in grapefruit juice preparations according to one study,[119] although other investigators deny its existence.[104] Bergapten is also found in Seville (sour) orange juice.[9] Bergapten's mechanism-based inhibition of CYP3A4 has been shown *in vitro*, albeit with only about one-third of the potency of that reported for 6′,7′-dihydroxybergamottin.[104] However, as one grapefruit juice preparation that had no detectable levels of bergapten significantly increased the AUC and C_{max} of felodipine,[104] bergapten is unlikely to be a major active ingredient in grapefruit juice-drug interactions.

Another bergamottin derivative, epoxybergamottin, has been reported to be present in grapefruit juice in only minor quantities.[9] Epoxybergamottin has also demonstrated mechanism-based inhibition of CYP3A4 *in vitro*,[12] but it is not chemically stable and is considered to be rapidly converted to 6′,7′-dihydroxybergamottin in the gastrointestinal tract.

Two dimers of furanocoumarins, GF-I-1 [1] and GF-I-4 [2], are minor components in grapefruit juice. They are reported to reduce CYP3A4 activities through both competitive and mechanism-based inhibition over 100 times more potently than 6′,7′-dihydroxybergamottin or bergamottin *in vitro*,[9,120] but further information on these two dimers, including clinical data, are unfortunately lacking.

Given the available data on flavonoids and furanocoumarins and the fact that the contents of the various individual species obviously differ among grapefruit juices,[9] it is possible that the combined effects of all forms of furanocoumarins acting together might contribute to the mechanism-based inhibition of intestinal CYP3A4 *in vivo*. There is also a possibility that other furanocoumarins could be newly identified as causative agents.

4.2 Candidate Ingredients for P-Glycoprotein Inhibition

Although naringin and naringenin have been shown to inhibit the transport of P-glycoprotein substrates *in vitro*,[18,27,121] there is insufficient information available to evaluate whether these flavonoids are the main inhibitory ingredients in grapefruit juice. It should be borne in mind that

1 GF-I-1 (4-[[6-hydroxy-7-[[1-[(1-hydroxy-1-methyl)ethyl]-4-methyl-6-(7-oxo-7*H*-furo[3,2-g][1]benzopyran-4-yl)-4-hexenyl]oxy]-3,7-dimethyl-2-octenyl]oxy]-7*H*-furo[3,2-g][1]benzopyran-7-one)
2 GF-I-4 (4-[[6-hydroxy-7-[[4-methyl-1-(1-methylethenyl)-6-(7-oxo-7*H*-furo[3,2-g][1]benzopyran-4-yl)-4-hexenyl]-xy]3,7-dimethyl-2-octenyl]xy]7*H*-furo[3,2-g][1]benzopyran-7-one)

these substances are not present in orange juice, which does have inhibitory effects on P-glycoprotein function.[111]

Some furanocoumarins, such as 6′,7′-dihydroxybergamottin, bergamottin and bergapten, have also been shown to inhibit transport of P-glycoprotein substrates *in vitro*.[27,119,121,122] However, this might not be relevant *in vivo* because *in vitro* data suggest that the major effect of 6′,7′-dihydroxybergamottin is attributable to inhibition of CYP3A4[121] and furanocoumarins are also present in Seville (sour) orange juice,[9] which is considered not to affect the function of P-glycoprotein.

In vitro studies employing fractionation of grapefruit juice suggest that the major P-glycoprotein inhibitors may be different from the major CYP3A4 inhibitors.[18,119] Polymethoxyflavones such as noblletin, heptamethoxyflavone and tangeretine, which are ingredients in orange juice, have been reported to inhibit the function of P-glycoprotein *in vitro*.[122,123] These compounds are also found in grapefruit juice in lower levels than in orange juice[124] and are known not to inhibit CYP3A4 *in vitro*.[123]

5. Conclusions

Since the effects of grapefruit juice on 19 drugs were reported in two reviews published in 1998,[3,4] 25 different drugs whose AUC and C_{max} are influenced by grapefruit juice have been newly reported. The outcomes in most cases were increases in these parameters, but decreases were reported for six drugs. The increases in AUC or C_{max} were probably due to mechanism-based inactivation of intestinal CYP3A4, with a possible minor contribution from decreased P-glycoprotein function; the decreases in AUC or C_{max} may have been due to inhibition of intestinal OATP. Other citrus juices, such as Seville (sour) orange juice and orange juice (sweet), have also been found to exert inhibitory effects. However, no specific ingredients in citrus juice have yet been established to have effects on AUC and C_{max} *in vivo*, although furanocoumarins are considered to be the most likely candidates.

Given the complexity of citrus juice-drug interactions and the wide range of drugs affected, we recommend that patients and healthcare providers avoid any citrus juice intake when taking medications until adverse effects due to possible interactions have been ruled out in clinical studies.

Furthermore, since the effect of grapefruit juice on intestinal CYP3A4 is known to continue for more than 24 hours, it might also be necessary to caution against citrus juice intake for at least 1 day before medication is taken. Furthermore, the elderly should be carefully cautioned about the need to avoid concomitant intake of grapefruit juice.

Acknowledgements

This work was supported by a grant from the Ministry of Health, Labour and Welfare, Japan. The authors have no conflicts of interest directly relevant to the content of this manuscript.

References

1. Henderson L, Yue QY, Bergquist C, et al. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002; 54: 349-56
2. Bailey DG, Spence JD, Munoz C, et al. Interaction of citrus juices with felodipine and nifedipine. Lancet 1991; 337: 268-9
3. Bailey DG, Malcolm J, Arnold O, et al. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998; 46: 101-10
4. Fuhr U. Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. Drug Saf 1998; 18: 251-72
5. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997; 99: 2545-53
6. Silverman RB. Mechanism-based enzyme inactivation: chemistry and enzymology. Vol. 1. Boca Raton (FL): CRC Press, 1988: 224
7. Silverman RB. Mechanism-based enzyme inactivation: chemistry and enzymology. Vol. 2. Boca Raton (FL): CRC Press, 1988: 288
8. Chan WK, Nguyen LT, Miller VP, et al. Mechanism-based inactivation of human cytochrome P450 3A4 by grapefruit juice and red wine. Life Sci 1998; 62: PL135-42
9. Guo LQ, Fukuda K, Ohta T, et al. Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. Drug Metab Dispos 2000; 28: 766-71
10. Bailey DG, Dresser GK, Bend JR. Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice. Clin Pharmacol Ther 2003; 73: 529-37
11. Schmiedlin Ren P, Edwards DJ, Fitzsimmons ME, et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents: decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. Drug Metab Dispos 1997; 25: 1228-33
12. Bailey DG, Dresser GK, Kreeft JH, et al. Grapefruit-felodipine interaction: effect of unprocessed fruit and probable active ingredients. Clin Pharmacol Ther 2000; 68: 468-77
13. Silverman JA. Multidrug-resistance transporters. Pharm Biotechnol 1999; 12: 353-86
14. Rashid TJ, Martin U, Clarke H, et al. Factors affecting the absolute bioavailability of nifedipine. Br J Clin Pharmacol 1995; 40: 51-8

15. Kupferschmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998; 45: 355-9
16. Kupferschmidt HH, Ha HR, Ziegler WH, et al. Interaction between grapefruit juice and midazolam in humans. Clin Pharmacol Ther 1995; 58: 20-8
17. Ducharme MP, Warbasse LH, Edwards DJ. Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. Clin Pharmacol Ther 1995; 57: 485-91
18. Takanaga H, Ohnishi A, Matsuo H, et al. Inhibition of vinblastine efflux mediated by P-glycoprotein by grapefruit juice components in caco-2 cells. Biol Pharm Bull 1998; 21: 1062-6
19. Xu J, Go ML, Lim LY. Modulation of digoxin transport across Caco-2 cell monolayers by citrus fruit juices: lime, lemon, grapefruit, and pummelo. Pharm Res 2003; 20: 169-76
20. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003; 42: 59-98
21. Lown KS, Mayo RR, Leichtman AB, et al. Role of intestinal P-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine. Clin Pharmacol Ther 1997; 62: 248-60
22. Edwards DJ, Fitzsimmons ME, Schuetz EG, et al. 6′,7′-dihydroxybergamottin in grapefruit juice and Seville orange juice: effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein. Clin Pharmacol Ther 1999; 65: 237-44
23. Parker RB, Yates CR, Soberman JE, et al. Effects of grapefruit juice on intestinal P-glycoprotein: evaluation using digoxin in humans. Pharmacotherapy 2003; 23: 979-87
24. Becquemont L, Verstuyft C, Kerb R, et al. Effect of grapefruit juice on digoxin pharmacokinetics in humans. Clin Pharmacol Ther 2001; 70: 311-6
25. Beveridge T, Nuesch E, Ohnhaus EE. Absolute bioavailability of digoxin tablets. Arzneimittel Forschung 1978; 28: 701-3
26. Cohen AF, Kroon R, Schoemaker HC, et al. The bioavailability of digoxin from three oral formulations measured by a specific h.p.l.c. assay. Br J Clin Pharmacol 1993; 35: 136-42
27. Dresser GK, Bailey DG, Leake BF, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 2002; 71: 11-20
28. Lilja JJ, Backman JT, Laitila J, et al. Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. Clin Pharmacol Ther 2003; 73: 192-8
29. Dresser GK, Bailey DG. The effects of fruit juices on drug disposition: a new model for drug interactions. Eur J Clin Invest 2003; 33 Suppl. 2: 10-6
30. Clifford CP, Adams DA, Murray S, et al. The cardiac effects of terfenadine after inhibition of its metabolism by grapefruit juice. Eur J Clin Pharmacol 1997; 52: 311-5
31. Ebert U, Oertel R, Kirch W. Influence of grapefruit juice on scopolamine pharmacokinetics and pharmacodynamics in healthy male and female subjects. Int J Clin Pharmacol Ther 2000; 38: 523-31
32. Lilja JJ, Kivisto KT, Backman JT, et al. Grapefruit juice substantially increases plasma concentrations of buspirone. Clin Pharmacol Ther 1998; 64: 655-60
33. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. Clin Pharmacol Ther 1998; 64: 477-83
34. Kantola T, Kivisto KT, Neuvonen PJ. Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. Clin Pharmacol Ther 1998; 63: 397-402
35. Schubert W, Cullberg G, Edgar B, et al. Inhibition of 17 beta-estradiol metabolism by grapefruit juice in ovariectomized women. Maturitas 1994; 20: 155-63
36. Takanaga H, Ohnishi A, Murakami H, et al. Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. Clin Pharmacol Ther 2000; 67: 201-14
37. Fuhr U, Maier Bruggemann A, Blume H, et al. Grapefruit juice increases oral nimodipine bioavailability. Int J Clin Pharmacol Ther 1998; 36: 126-32
38. Soons PA, Vogels BA, Roosemalen MC, et al. Grapefruit juice and cimetidine inhibit stereoselective metabolism of nitrendipine in humans. Clin Pharmacol Ther 1991; 50: 394-403
39. Fingerova H, Oborna I, Petrova P, et al. Does grapefruit juice increase the bioavailability of orally administered sex steroids? [in Czech]. Ceska Gynekol 2003; 68: 117-21
40. Charbit B, Becquemont L, Lepere B, et al. Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. Clin Pharmacol Ther 2002; 72: 514-23
41. Di Marco MP, Edwards DJ, Wainer IW, et al. 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
42. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. Clin Pharmacol Ther 1999; 66: 118-27
43. Edgar B, Bailey D, Bergstrand R, et al. 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
44. Munoz CE, Ito S, Bend JR, et al. Propafenone interaction with CYP3A4 inhibitors in man [abstract]. Clin Pharmacol Ther 1997; 61: 154
45. Uno T, Ohkubo T, Sugawara K, et al. Effects of grapefruit juice on the stereoselective disposition of nicardipine in humans: evidence for dominant presystemic elimination at the gut site. Eur J Clin Pharmacol 2000; 56: 643-9
46. Veronese ML, Gillen LP, Burke JP, et al. Exposure-dependent inhibition of intestinal and hepatic CYP3A4 in vivo by grapefruit juice. J Clin Pharmacol 2003; 43: 831-9
47. Fuhr U, Muller Peltzer H, Kern R, et al. Effects of grapefruit juice and smoking on verapamil concentrations in steady state. Eur J Clin Pharmacol 2002; 58: 45-53
48. Kanazawa S, Ohkubo T, Sugawara K. The effects of grapefruit juice on the pharmacokinetics of erythromycin. Eur J Clin Pharmacol 2001; 56: 799-803
49. Desta Z, Kivisto KT, Lilja JJ, et al. Stereoselective pharmacokinetics of cisapride in healthy volunteers and the effect of repeated administration of grapefruit juice. Br J Clin Pharmacol 2001; 52: 399-407
50. Weber A, Jager R, Borner A, et al. Can grapefruit juice influence ethinylestradiol bioavailability? Contraception 1996; 53: 41-7
51. Sigusch H, Hippius M, Henschel L, et al. Influence of grapefruit juice on the pharmacokinetics of a slow release nifedipine formulation. Pharmazie 1994; 49: 522-4
52. Lilja JJ, Kivisto KT, Backman JT, et al. Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life. Eur J Clin Pharmacol 2000; 56: 411-5
53. Hollander AA, van Rooij J, Lentjes GW, et al. The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients [abstract]. Clin Pharmacol Ther 1995; 57: 318-24
54. Libersa CC, Brique SA, Motte KB, et al. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. Br J Clin Pharmacol 2000; 49: 373-8
55. Garg SK, Kumar N, Bhargava VK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. Clin Pharmacol Ther 1998; 64: 286-8

56. Ozdemir M, Aktan Y, Boydag BS, et al. Interaction between grapefruit juice and diazepam in humans. Eur J Drug Metab Pharmacokinet 1998; 23: 55-9
57. Castro N, Jung H, Medina R, et al. Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 2002; 46: 1614-6
58. Varis T, Kivisto KT, Neuvonen PJ. Grapefruit juice can increase the plasma concentrations of oral methylprednisolone. Eur J Clin Pharmacol 2000; 56: 489-93
59. Fuhr U, Klittich K, Staib AH. Inhibitory effect of grapefruit juice and its bitter principal, naringenin, on CYP1A2 dependent metabolism of caffeine in man. Br J Clin Pharmacol 1993; 35: 431-6
60. van Agtmael MA, Gupta V, van der Graaf CA, et al. The effect of grapefruit juice on the time-dependent decline of artemether plasma levels in healthy subjects. Clin Pharmacol Ther 1999; 66: 408-14
61. Lee AJ, Chan WK, Harralson AF, et al. The effects of grapefruit juice on sertraline metabolism: an in vitro and in vivo study. Clin Ther 1999; 21: 1890-9
62. Ho PC, Chalcroft SC, Coville PF, et al. Grapefruit juice has no effect on quinine pharmacokinetics. Eur J Clin Pharmacol 1999; 55: 393-8
63. Josefsson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. Eur J Clin Pharmacol 1996; 51: 189-93
64. Vincent J, Harris SI, Foulds G, et al. Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. Br J Clin Pharmacol 2000; 50: 455-63
65. Yasui N, Kondo T, Furukori H, et al. Effects of repeated ingestion of grapefruit juice on the single and multiple oral-dose pharmacokinetics and pharmacodynamics of alprazolam. Psychopharmacology (Berl) 2000; 150: 185-90
66. Min DI, Ku YM, Geraets DR, et al. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of quinidine in healthy volunteers. J Clin Pharmacol 1996; 36: 469-76
67. Penzak SR, Acosta EP, Turner M, et al. Effect of Seville orange juice and grapefruit juice on indinavir pharmacokinetics. J Clin Pharmacol 2002; 42: 1165-70
68. Shelton MJ, Wynn HE, Hewitt RG, et al. Effects of grapefruit juice on pharmacokinetic exposure to indinavir in HIV-positive subjects. J Clin Pharmacol 2001; 41: 435-42
69. Cheng KL, Nafziger AN, Peloquin CA, et al. Effect of grapefruit juice on clarithromycin pharmacokinetics. Antimicrob Agents Chemother 1998; 42: 927-9
70. Vandel P, Regina W, Reix I, et al. Grapefruit juice as a contraindication? An approach in psychiatry [in French]. Encephale 1999; 25: 67-71
71. Yasui N, Kondo T, Suzuki A, et al. Lack of significant pharmacokinetic interaction between haloperidol and grapefruit juice. Int Clin Psychopharmacol 1999; 14: 113-8
72. Tassaneeyakul W, Vannaprasaht S, Yamazoe Y. Formation of omeprazole sulphone but not 5-hydroxyomeprazole is inhibited by grapefruit juice. Br J Clin Pharmacol 2000; 49: 139-44
73. Christensen H, Asberg A, Holmboe AB, et al. Coadministration of grapefruit juice increases systemic exposure of diltiazem in healthy volunteers. Eur J Clin Pharmacol 2002; 58: 515-20
74. Sigusch H, Henschel L, Kraul H, et al. Lack of effect of grapefruit juice on diltiazem bioavailability in normal subjects. Pharmazie 1994; 49: 675-9
75. Jetter A, Kinzig Schippers M, Walchner Bonjean M, et al. Effects of grapefruit juice on the pharmacokinetics of sildenafil. Clin Pharmacol Ther 2002; 71: 21-9
76. Zaidenstein R, Soback S, Gips M, et al. Effect of grapefruit juice on the pharmacokinetics of losartan and its active metabolite E3174 in healthy volunteers. Ther Drug Monit 2001; 23: 369-73
77. Lane HY, Jann MW, Chang YC, et al. Repeated ingestion of grapefruit juice does not alter clozapine's steady-state plasma levels, effectiveness, and tolerability. J Clin Psychiatry 2001; 62: 812-7
78. Vandel S, Netillard C, Perault MC, et al. Plasma levels of clozapine and desmethylclozapine are unaffected by concomitant ingestion of grapefruit juice. Eur J Clin Pharmacol 2000; 56: 347-8
79. van Rooij J, van der Meer FJM, Schoemaker HC, et al. Comparison of the effect of grapefruit juice and cimetidine on pharmacokinetics and anticoagulant effect of a single dose of acenocoumarol [abstract]. Br J Clin Pharmacol 1993; 35: 548
80. Kumar N, Garg SK, Prabhakar S. Lack of pharmacokinetic interaction between grapefruit juice and phenytoin in healthy male volunteers and epileptic patients. Methods Find Exp Clin Pharmacol 1999; 21: 629-32
81. Fukazawa I, Uchida N, Uchida E, et al. Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. Br J Clin Pharmacol 2004; 57: 448-55
82. Banfield C, Gupta S, Marino M, et al. Grapefruit juice reduces the oral bioavailability of fexofenadine but not desloratadine. Clin Pharmacokinet 2002; 41: 311-8
83. Penzak SR, Gubbins PO, Gurley BJ, et al. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. Ther Drug Monit 1999; 21: 304-9
84. Demarles D, Gillotin C, Bonaventure Paci S, et al. Single-dose pharmacokinetics of amprenavir coadministered with grapefruit juice. Antimicrob Agents Chemother 2002; 46: 1589-90
85. Reif S, Nicolson MC, Bisset D, et al. Effect of grapefruit juice intake on etoposide bioavailability. Eur J Clin Pharmacol 2002; 58: 491-4
86. Gupta MC, Garg SK, Badyal D, et al. Effect of grapefruit juice on the pharmacokinetics of theophylline in healthy male volunteers. Methods Find Exp Clin Pharmacol 1999; 21: 679-82
87. Mayol RF, Adamson DS, Gammans RE, et al. Pharmacokinetics and disposition of ^{14}C-buspirone HCl after intravenous and oral dosing in man [abstract]. Clin Pharmacol Ther 1985; 37: 210
88. Kivisto KT, Lamberg TS, Neuvonen PJ. Interactions of buspirone with itraconazole and rifampicin: effects on the pharmacokinetics of the active 1-(2-pyrimidinyl)-piperazine metabolite of buspirone. Pharmacol Toxicol 1999; 84: 94-7
89. Bailey DG. Grapefruit juice-drug interaction issues. In: Boullata J, Armeni V, editors. Handbook of drug-nutrient interactions. Totawa (NJ): The Humana Press, 2004: 175-194
90. Rogers JD, Zhao J, Liu L, 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
91. Willner K. Excretion and decomposition of 3-methoxy-N-methylmorphinan and its demethylated derivatives in man [in German]. Arzneimittel Forschung 1963; 13: 26-9
92. Talajic M, DeRoode MR, Nattel S. Comparative electrophysiologic effects of intravenous amiodarone and desethylamiodarone in dogs: evidence for clinically relevant activity of the metabolite. Circulation 1987; 75: 265-71
93. Zhou L, Chen BP, Kluger J, et al. Effects of amiodarone and its active metabolite desethylamiodarone on the ventricular defibrillation threshold. J Am Coll Cardiol 1998; 31: 1672-8
94. 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
95. Brunner LJ, Pai KS, Munar MY, et al. Effect of grapefruit juice on cyclosporin A pharmacokinetics in pediatric renal transplant patients. Pediatr Transplant 2000; 4: 313-21
96. Hermann M, Asberg A, Reubsaet JL, et al. Intake of grapefruit juice alters the metabolic pattern of cyclosporin A in renal

transplant recipients. Int J Clin Pharmacol Ther 2002; 40: 451-6

97. Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. Clin Pharmacokinet 2000; 38: 111-80
98. Kaukonen KM, Olkkola KT, Neuvonen PJ. Fluconazole but not itraconazole decreases the metabolism of losartan to E-3174. Eur J Clin Pharmacol 1998; 53: 445-9
99. Lippert C, Ling J, Brown P, et al. Mass balance and pharmacokinetics of MDL 16455A in healthy male volunteers [abstract]. Pharm Res 1995; 12: S390
100. Gubbins PO, McConnell SA, Gurley BJ, et al. Influence of grapefruit juice on the systemic availability of itraconazole oral solution in healthy adult volunteers. Pharmacotherapy 2004; 24: 460-7
101. Dresser GK, Bailey DG, Carruthers SG. Grapefruit juice: felodipine interaction in the elderly. Clin Pharmacol Ther 2000; 68: 28-34
102. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs 2004; 4: 281-97
103. Lilja JJ, Juntti-Patinen L, Neuvonen PJ. Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. Clin Pharmacol Ther 2004; 75: 184-90
104. Malhotra S, Bailey DG, Paine MF, et al. Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins. Clin Pharmacol Ther 2001; 69: 14-23
105. Backman JT, Maenpaa J, Belle DJ, et al. Lack of correlation between in vitro and in vivo studies on the effects of tangeretin and tangerine juice on midazolam hydroxylation. Clin Pharmacol Ther 2000; 67: 382-90
106. Silverman JA, Thorgeirsson SS. Regulation and function of the multidrug resistance genes in liver. Prog Liver Dis 1995; 13: 101-23
107. Cvetkovic M, Leake B, Fromm MF, et al. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. Drug Metab Dispos 1999; 27: 866-71
108. Kim RB. Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. Eur J Clin Invest 2003; 33 Suppl. 2: 1-5
109. Ranganna S, Govindarajan VS, Ramana KV. Citrus fruits: varieties, chemistry, technology, and quality evaluation. Part II: chemistry, technology, and quality evaluation. A. Chemistry. Crit Rev Food Sci Nutr 1983; 18: 313-86
110. Bailey DG, Arnold JM, Spence JD. Grapefruit juice and drugs: how significant is the interaction? Clin Pharmacokinet 1994; 26: 91-8
111. Kuhnau J. The flavonoids: a class of semi-essential food components: their role in human nutrition. World Rev Nutr Diet 1976; 24: 117-91
112. Cheng KJ, Krishnamurty HG, Jones GA, et al. Identification of products produced by the anaerobic degradation of naringin by Butyrivibrio sp. C3. Can J Microbiol 1971; 17: 129-31
113. Fuhr U, Kummert AL. The fate of naringin in humans: a key to grapefruit juice-drug interactions? Clin Pharmacol Ther 1995; 58: 365-73
114. Bailey DG, Arnold JM, Munoz C, et al. Grapefruit juice: felodipine interaction. Mechanism, predictability, and effect of naringin. Clin Pharmacol Ther 1993; 53: 637-42
115. Bailey DG, Arnold JM, Strong HA, et al. Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. Clin Pharmacol Ther 1993; 54: 589-94
116. Bailey DG, Munoz C, Arnold JMO, et al. Grapefruit juice and naringin interaction with nitrendipine [abstract]. Clin Pharmacol Ther 1992; 51: 156
117. Bailey DG, Kreeft JH, Munoz C, et al. Grapefruit juice-felodipine interaction: effect of naringin and 6′,7′-dihydroxybergamottin in humans. Clin Pharmacol Ther 1998; 64: 248-56
118. Kakar SM, Paine MF, Stewart PW, et al. 6′7′-Dihydroxybergamottin contributes to the grapefruit juice effect. Clin Pharmacol Ther 2004; 75: 569-79
119. Ohnishi A, Matsuo H, Yamada S, et al. Effect of furanocoumarin derivatives in grapefruit juice on the uptake of vinblastine by Caco-2 cells and on the activity of cytochrome P450 3A4. Br J Pharmacol 2000; 130: 1369-77
120. Tassaneeyakul W, Guo LQ, Fukuda K, et al. Inhibition selectivity of grapefruit juice components on human cytochromes P450. Arch Biochem Biophys 2000; 378: 356-63
121. Eagling VA, Profit L, Back DJ. Inhibition of the CYP3A4-mediated metabolism and P-glycoprotein-mediated transport of the HIV-1 protease inhibitor saquinavir by grapefruit juice components. Br J Clin Pharmacol 1999; 48: 543-52
122. Ikegawa T, Ushigome F, Koyabu N, et al. Inhibition of P-glycoprotein by orange juice components, polymethoxyflavones in adriamycin-resistant human myelogenous leukemia (K562/ADM) cells. Cancer Lett 2000; 160: 21-8
123. Takanaga H, Ohnishi A, Yamada S, et al. Polymethoxylated flavones in orange juice are inhibitors of P-glycoprotein but not cytochrome P450 3A4. J Pharmacol Exp Ther 2000; 293: 230-6
124. Manthey JA, Grohmann K. Phenols in citrus peel byproducts: concentrations of hydroxycinnamates and polymethoxylated flavones in citrus peel molasses. J Agric Food Chem 2001; 49: 3268-73

Correspondence and offprints: Mr *Mitsuo Saito*, Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-8501, Japan.
E-mail: m-saito@nihs.go.jp

Eur J Clin Pharmacol (2005) 61: 531–536
DOI 10.1007/s00228-005-0974-x

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Mitsuo Saito · Mutsuko Hirata-Koizumi
Shinji Miyake · Ryuichi Hasegawa

Comparison of information on the pharmacokinetic interactions of Ca antagonists in the package inserts from three countries (Japan, USA and UK)

Received: 27 February 2005 / Accepted: 24 June 2005 / Published online: 23 July 2005

Abstract *Objective*: Ca antagonists are one of the most popular classes of drugs used to treat hypertension and angina. These drugs may interact with either CYP3A4 or MDR-1 substrates, with the degree of interaction differing with each drug. We carried out a literature search to examine and compare the extent to which crucial pharmacokinetic (PK) information is included in package inserts (PIs) in Japan, USA and the UK.
Methods: A MEDLINE search from 1966 to November 2004 was undertaken with the aim of identifying studies on clinical PK drug interactions between seven Ca antagonists that are available in three countries and three CYP3A4 inhibitors (erythromycin, itraconazole and cimetidine), a CYP3A4 inhibitory food, grapefruit juice (GFJ) and the MDR-1 substrate, digoxin. The current PIs for Ca antagonists were obtained from the website of the regulatory authorities or the electronic Medicines Compendium.
Results: Of all possible combinations of seven Ca antagonists with three CYP3A4 inhibitor drugs, drug interaction information was available in the literature on nine combinations: Seven of these were listed in the USA PIs, two in the UK PIs, and none in the Japanese PIs. Interaction studies with GFJ were reported for every Ca antagonist; PIs in the USA provided quantitative data for four of these interactions, whereas UK PIs provided quantitative data for only one of the interactions and Japanese PIs provided no quantitative information. The PK data of co-medication of digoxin with Ca antagonists have been reported for every Ca antagonists. The USA PIs provided quantitative data for five Ca antagonists, whereas the UK PIs provided quantitative data for three Ca antagonists and Japanese PIs provided no quantitative data.
Conclusion: The literature search revealed that PIs in the USA provided a great deal of quantitative information on PK interactions between Ca antagonists and other drugs or GFJ. In contrast, PIs in the UK and Japan did not provide sufficient information. We conclude that crucial quantitative information on these drug interactions should be incorporated in PIs, especially in Japan and the UK, as a means of assisting healthcare providers.

Keywords Package inserts · Ca antagonists · Drug interaction · Grapefruit juice · CYP3A4 inhibitor · Digoxin

M. Saito (✉) · M. Hirata-Koizumi · S. Miyake · R. Hasegawa
Division of Medicinal Safety Science,
National Institute of Health Sciences,
1-18-1 Kamiyoga, Setagaya-ku,
Tokyo
158-8501 Japan
E-mail: m-saito@nihs.go.jp
Tel.: +81-3-37009653
Fax: +81-3-37009788

Introduction

The majority of Ca antagonists function as the substrate and inhibitor of both CYP3A4 and MDR-1 [1, 2]. In order to evaluate available information on pharmacokinetic (PK) interactions, we selected three representative CYP3A4 inhibitory drugs, itraconazole, erythromycin and cimetidine, a CYP3A4 inhibitory food, grapefruit juice (GFJ), and digoxin, which is a substrate for CYP3A4 but not for MDR-1, and carried out a literature on clinical PK interactions between Ca antagonists and these CYP3A4 inhibitory drugs and GFJ. We then compared how this information is reflected in package inserts (PIs) in Japan, USA and the UK.

Methods

The PIs used currently in Japan were obtained from the website of the Pharmaceuticals and Medical Device Agency (http://www.pmda.go.jp), the USA PIs were obtained from the Federal Drug Administration (FDA) website (http://www.fda.gov) and the UK PIs were obtained from the electronic Medicines Compendium (http://emc.medicines.org.uk) and British National

Formulary website (http://www.bnf.org/bnf/index.htm). According to the website of the European Medicines Agency (EMEA), there is no centralized authorization of Ca antagonists in the European Union. Each website was accessed in November 2004. The literature search was conducted using MEDLINE from 1966 to November 2004 with the aim of identifying studies on clinical PK interactions between Ca antagonists and either CYP inhibitors, GFJ or digoxin. We collected information on the AUC (area under the blood concentration-time curve), C_{max} (maximum blood concentration) and pharmacodynamic (PD) effects of the co-administration of Ca antagonists and CYP inhibitors or GFJ. As our initial literature search revealed a scarcity of information on digoxin-Ca antagonist interactions, we subsequently directed our search to obtaining PK information on digoxin, including steady-state plasma concentration (C_{ss}), trough level, AUC and C_{max}.

Results

Analysis of the drug PIs showed that at the time of this investigation 18 types of dihydropyridine derivatives were available in the three countries: 14 in Japan, seven in the USA and nine in the UK. Nine drugs, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, efonidipine, manidipine, nilvadipine and nitrendipine, were available only in Japan; two drugs, lacidipine and lercanidipine, were available only in the UK; two drugs, isradipine and nimodipine, were available only in the UK and USA. Only five drugs, amlodipine, felodipine, nicardipine, nifedipine and nisoldipine, were available in all three countries. Both of the non-dihydropyridine derivatives, verapamil and diltiazem, were available in all three countries. We consequently focused on these seven drugs common to three countries.

Effect of the CYP3A4 inhibitors, erythromycin, itraconazole and cimetidine, on the pharmacokinetics of Ca antagonists (Table 1)

Dihydropyridine derivatives

Of the 15 combinations of five Ca antagonists (dihydropyridine derivatives) and three CYP3A4 inhibitors that we studied, PK information on seven combinations

Table 1 PK information on CYP3A4 inhibitor-Ca antagonist interactions and the description on the PI

		Literature information				Quantitative data in package inserts[a]		
	CYP3A4 inhibitors	AUC	C_{max}	Adverse effects/PD[a]	Reference	Japan	USA	UK
Dihydropyridines								
Amlodipine	Erythromycin itraconazole	No data	No data			–	–	–
	Cimetidine	No effect	No effect		[6][b]	–	No effect	No effect
Felodipine	Erythromycin	2.5-fold	2.3-fold	Palpitations, flushing, etc.	[7, 8]	–	2.5-fold (AUC and C_{max})	–
	Itraconazole	6.3-fold	7.8-fold	Increased HR, lower BP	[9, 10]	–	AUC: eightfold; C_{max}: more than sixfold	–
	Cimetidine	1.6-fold	1.6-fold		[11]	–	AUC and C_{max}: 1.5-fold	–
Nicardipine	Erythromycin itraconazole cimetidine	No data	No data			–	–	–
Nifedipine	Erythromycin	No data	No data			–	–	–
	Itraconazole	4.4-fold in trough		Peripheral edema	[12][c]	–	–	–
	Cimetidine	1.8-fold	1.8-fold	Increased effect and HR	[13, 14]	–	–	–
Nisoldipine	Erythromycin itraconazole	No data	No data			–	–	–
	Cimetidine	1.3-fold	1.5-fold	Not effect	[15, 16]	–	AUC and C_{max}: 1.3- to 1.45-fold	–
Others								
Verapamil	Erythromycin itraconazole	No data	No data			–	–	–
	Cimetidine	No effect to 1.4-fold	No effect to 1.4-fold	No effect to increased effect	[17, 18]	–	Reduced or unchanged clearance	–
Diltiazem	Erythromycin itraconazole	No data	No data			–	–	–
	Cimetidine	1.5-fold	1.6-fold		[19]	–	AUC: 1.53-fold; C_{max}: 1.58-fold	–

[a]–; No data provided; HR, heart rate; BP, blood pressure
[b]A review of cited company data. Original data was not published
[c]Case report

was available in the literature. Some of the combinations were accompanied by significant PD effects, such as edema and increased heart rate.

The Japanese PIs for amlodipine did not mention interactions with any of the CYP inhibitors included in this study, whereas in the USA and UK, the PIs for amlodipine stated that no interaction with cimetidine had been found. The PIs for felodipine from all three countries listed all CYP inhibitors in the precautions/interaction section, but only the USA PIs provided quantitative data. PIs for nicardipine from all three countries listed cimetidine in the precautions/interaction section, but no data were provided in any of the PIs. The UK PIs for nifedipine listed all three CYP inhibitors, Japan listed itraconazole and cimetidine, while the USA listed only cimetidine; none of these PIs contained quantitative data. PIs for nisoldipine from all three countries listed cimetidine in the precautions/interaction section, but again, only the USA PIs provided data. The UK PIs listed itraconazole in the contraindications section without any quantitative data.

Non-dihydropyridine derivatives (verapamil and diltiazem)

While there is some controversy regarding the interaction between cimetidine and verapamil, cimetidine has been shown to increase the AUC and C_{max} of diltiazem. There was no information in the literature on known interactions of verapamil and diltiazem with either erythromycin or itraconazole.

With respect to interactions with verapamil, the Japanese PI listed itraconazole and the UK PI listed cimetidine, both without any quantitative data, while cimetidine was listed in the USA PI with quantitative data. This PI also mentioned "CYP inhibitors", with erythromycin being cited as an example, although no additional details were provided. Itraconazole was not specified in the USA PI. The PIs for diltiazem from all three countries listed cimetidine in the precautions/interaction section, but only in the USA PI was the precautions/interaction section accompanied by quantitative data.

Effect of GFJ on the PK of Ca antagonists (Table 2)

Dihydropyridine derivatives

Our literature search revealed information on PD interactions between GFJ and all five dihydropyridine derivatives, with the enhancement of the blood pressure-lowering effect being noted for felodipine, nicardipine and nisoldipine. While the effect of GFJ on the PK of amlodipine was minimal, GFJ did cause a marked increase in the AUC and C_{max} of the other Ca antagonists.

GFJ was not mentioned in the Japanese PIs for amlodipine, whereas the USA and UK PIs provided information on GFJ, with a brief summary of an interaction study in the "Special Studies" section. For felodipine, nifedipine and nisoldipine, the PIs from all three countries mentioned interactions with GFJ, but only the USA PI provided quantitative information. For nicardipine, the USA PI did not mention GFJ, whereas both Japanese and UK PIs listed interactions with GFJ without providing any quantitative data.

Verapamil and diltiazem

Although data from the literature on the effect of GFJ on verapamil are controversial, one study showed that increases in the AUC and C_{max} and a prolongation of the PR interval in cardiograms are associated with this

Table 2 PK information on grapefruit juice-Ca antagonist interactions and the description in the PI

	Literature Information[a]				Quantitative data in PIs[a]		
	AUC	C_{max}	Adverse effects/PD	Reference	Japan	USA	UK
Dihydropyridines							
Amlodipine	1.2 fold	1.2-fold	No effect on BP and HR	[20]	–	No effect	No effect
Felodipine	1.7- to 2.9 fold	2.7- to 4.0-fold	Lower diastolic BP, and higher HR	[7, 21]	–	More than twofold increase in AUC and C_{max}	–
Nicardipine	1.6-fold	No data	Higher HR	[22]	–	–	–
Nifedipine	Twofold	1.9-fold		[23]	–	Twofold increase in AUC and C_{max}	–
Nisoldipine	2.0- to 4.1-fold	4.1- to 4.9-fold	Decreased systolic and diastolic BP	[24, 25]	–	AUC: two to fivefold; C_{max}: three to sevenfold	–
Others							
Verapamil	No effect up to 1.5-fold	No effect up to 1.6-fold	Prolongation of PR interval in cardiograms	[26, 27]	–	–	–
Diltiazem	No effect up to 1.2-fold	No effect up to 1.2-fold	No effect on BP and HR	[28, 29]	–	–	–

[a]–, No data provided; HR, heart rate; BP, blood pressure

combination. The PIs in all countries listed GFJ in the interactions section without providing any quantitative information.

Our literature search revealed that diltiazem had only a minimal effect on the blood concentration of the Ca antagonist and no significant effect on pharmacological actions. GFJ was not listed in the PIs of any of the countries as a possible source of interaction.

Effect of Ca antagonists on the PKs of digoxin (Table 3)

Dihydropyridine derivatives

Information in the literature indicated that amlodipine did not alter either the C_{ss} or pharmacological effects of digoxin. Felodipine was reported to increase the C_{max} of digoxin, although the trough level and pharmacological action were not altered. One study reported that nicardipine did not significantly alter the AUC of digoxin, whereas another study showed that there was an increase in the plasma concentration of digoxin. Nifedipine increased the AUC and plasma concentration of digoxin, while nisoldipine increased the trough level with altered systolic time intervals.

The Japanese PI for amlodipine did not mention digoxin, whereas the USA and UK PIs stated that amlodipine did not alter serum digoxin level. For felodipine, the Japanese and UK PIs listed digoxin without any quantitative data, whereas the USA PI stated that no significant interaction was observed. All PIs for nicardipine and nifedipine listed digoxin without any supporting quantitative data. For nisoldipine, the Japanese PI listed digoxin without any quantitative data, whereas both the USA and UK PIs stated that no significant interaction was observed with this drug combination.

Verapamil and diltiazem

There are reports that verapamil increases various PK parameters of digoxin, whereas diltiazem only increases the AUC of digoxin.

The USA PI for verapamil listed digoxin accompanied with quantitative data, whereas both Japanese and UK PIs mentioned digoxin without any quantitative data. For diltiazem, all PIs listed digoxin with only the USA and UK PIs containing quantitative data.

For all of the possible combinations of the seven Ca antagonists studied with the three CYP3A4 inhibitor drugs, information on nine combinations was available in literature: seven were listed in USA PIs, one in the UK PI and none in the PI for Japan. Similarly, interaction studies with GFJ were reported for every Ca antagonist, and the PIs in the USA also provided quantitative data for four of the Ca antagonists, whereas quantitative data were provided for only one Ca antagonist in the UK PIs and no quantitative data were provided in the Japanese PIs. Japanese PIs merely expressed that GFJ "may increase plasma concentration" or cited experience with similar drugs as "coadministration of GFJ increased blood concentration of nifedipine". PK data on the co-medication of digoxin with Ca antagonists have been reported for every Ca antagonist. The USA PIs provided quantitative data for five drugs, whereas the UK PIs provided information for three and the Japanese PIs provided no information.

For drugs common to all three countries other than the seven specifically studied here, a small number of PIs provided quantitative interaction data: four for the USA, three for the UK and four for Japan.

Table 3 PK information on digoxin-Ca antagonist interactions and the description in the PIs

	Literature information: change in digoxin			Quantitative data for digoxin in PIs[a]		
	PK	PD	Reference	Japan	USA	UK
Dihydropyridines						
Amlodipine	Not significant (C_{ss})	No change	[30]	–	No change of serum level or renal clearance	No change in serum level or renal clearance
Felodipine	1.2- to 1.4-fold (C_{max}), unchanged trough	No change	[31, 32]	–	No change	–
Nicardipine	1.1-fold		[33]	–	–	–
Nifedipine	1.45-fold (plasma level)		[34]	–	–	–
Nisoldipine	1.15- fold (trough)	Altered systolic time intervals	[35]	–	No interaction	No interaction
Others						
Verapamil	1.6- to 1.8-fold (C_{ss}), 1.7-fold (plasma level)	Shortened systole time	[34, 36]	–	1.5- to 1.75-fold (Serum level)	–
Diltiazem	1.2-fold (AUC, C_{ss}), no effect (serum level)		[37, 38]	–	1.2-fold or no increase of serum level	Small increases in serum level

[a] –, No data provided

Discussion

Drug interactions are one of the most important issues to be considered for the safe and proper use of drugs. Quantitative data from clinical PK interaction studies may provide valuable information for predicting the adverse reactions that may occur with co-medication. However, a lack of critical information may make it very difficult for healthcare providers to have a clear understanding of what can be considered to be a potential interaction and, consequently, to choose suitable drugs within the same class.

Focusing on seven Ca antagonists available in all three countries, we carried out a thorough literature search in order to analyze the information available on potential PK interactions of these Ca antagonists with three specified CYP3A4 inhibitors, GFJ and digoxin. We found that PK data were available for only one-half of the possible combinations with the CYP3A4 inhibitors, while all of the combinations with GFJ or digoxin were fully documented. The major reasons for the limited number of clinical PK studies with CYP3A4 inhibitors may originate in the vast number of CYP3A4 substrate drugs and inhibitors on the market and because the interaction was easily predicted by in vitro studies. Two factors can help explain the extensiveness of the clinical PK studies on the interactions of Ca antagonists with GFJ: (1) the metabolic inhibition of GFJ on Ca antagonists in the intestinal wall is a relatively recent discovery; (2) the extent of the interaction is, in some cases, extremely high; for example, a more than tenfold increase in the simvastatin AUC following GFJ intake. With respect to the interaction of Ca antagonists with digoxin, there were also extensive studies, probably because the plasma concentration of digoxin is affected by MDR-1 substrates and the therapeutic range is very narrow.

The USA PIs contained considerable quantitative information even though most of the interaction studies had been reported following approval of the drugs. In contrast, the UK PIs provided quantitative information for a great many fewer drugs, and Japan PIs provided only general information on GFJ-Ca antagonist interactions, such as "GFJ may increase the blood concentration of the Ca antagonist", although they did list many interactive drug names in the precautionary section. In the case of Japan, the regulatory guidelines require that the PI be "as simple as possible", and do not obligate the license holders to reflect the result of "no effect" explicitly [3–5]. This might have lead to the non inclusion of literature data in the Japanese PIs. Therefore, it is likely that the descriptive differences of the PIs for each Ca antagonist between countries may reflect the differences in the attitude of the regulatory authorities.

In conclusion, we consider that it would be very helpful to healthcare providers to provide a minimal amount of clearly presented critical information in the drug PIs, even though detailed information is provided by the license holder via supplemental prescription aids such as interview forms, Summary of Product Characteristics (SPC) or European Public Assessment Reports (EPARs).

Acknowledgements This work was supported by a grant from the Ministry of Health, Labour and Welfare, Japan. The authors have no conflicts of interest directly relevant to the content of this manuscript.

References

1. Klotz U (2002) Interaction potential of lercanidipine, a new vasoselective dihydropyridine calcium antagonist. Arzneimittelforschung 52:155–161
2. Katoh M, Nakajima M, Yamazaki H, Yokoi T (2000) Inhibitory potencies of 1,4-dihydropyridine calcium antagonists to P-glycoprotein-mediated transport: comparison with the effects on CYP3A4. Pharm Res 17:1189–1197
3. Abernethy DR (1989) The pharmacokinetic profile of amlodipine. Am Heart J 118:1100–1103
4. Bailey DG, Bend JR, Arnold JM, Tran LT, Spence JD (1996) Erythromycin-felodipine interaction: magnitude, mechanism, and comparison with grapefruit juice. Clin Pharmacol Ther 60:25–33
5. Liedholm H, Nordin G (1991) Erythromycin-felodipine interaction. Drug Intell Clin Pharm 25:1007–1008
6. Jalava KM, Olkkola KT, Neuvonen PJ (1997) Itraconazole greatly increases plasma concentrations and effects of felodipine. Clin Pharmacol Ther 61:410–415
7. Neuvonen PJ, Suhonen R (1995) Itraconazole interacts with felodipine. J Am Acad Dermatol 33:134–135
8. Janzon K, Edgar B, Lundborg P, Regardh CG (1986) The influence of cimetidine and spinolactone on the pharmacokinetics and haemodynamics effects of felodipine in healthy subjects. Acta Pharmacol Toxicol 59 [Suppl 5]:98
9. Tailor SA, Gupta AK, Walker SE, Shear NH (1996) Peripheral edema due to nifedipine-itraconazole interaction: a case report. Arch Dermatol 132:350–352
10. Renwick AG, Le Vie J, Challenor VF, Waller DG, Gruchy B, George CF (1987) Factors affecting the pharmacokinetics of nifedipine. Eur J Clin Pharmacol 32:351–355
11. Schwartz JB, Upton RA, Lin ET, Williams RL, Benet LZ (1988) Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 43:673–680
12. Heinig R (1998) Clinical pharmacokinetics of nisoldipine coat-core. Clin Pharmacokinet 35:191–208
13. van Harten J, van Brummelen P, Lodewijks MT, Danhof M, Breimer DD (1988) Pharmacokinetics and hemodynamic effects of nisoldipine and its interaction with cimetidine. Clin Pharmacol Ther 43:332–341
14. Abernethy DR, Schwartz JB, Todd EL (1985) Lack of interaction between verapamil and cimetidine. Clin Pharmacol Ther 38:342–349
15. Mikus G, Eichelbaum M, Fischer C, Gumulka S, Klotz U, Kroemer HK (1990) Interaction of verapamil and cimetidine: stereochemical aspects of drug metabolism, drug disposition and drug action. J Pharmacol Exp Ther 253:1042–1048
16. Winship LC, McKenney JM, Wright JT Jr, Wood JH, Goodman RP (1985) The effect of ranitidine and cimetidine on single-dose diltiazem pharmacokinetics. Pharmacotherapy 5:16–19
17. Josefsson M, Zackrisson AL, Ahlner J (1996) Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. Eur J Clin Pharmacol 51:189–193
18. Dresser GK, Bailey DG, Carruthers SG (2000) Grapefruit juice-felodipine interaction in the elderly. Clin Pharmacol Ther 68:28–34

19. Uno T, Ohkubo T, Sugawara K, Higashiyama A, Motomura S, Ishizaki T (2000) Effects of grapefruit juice on the stereoselective disposition of nicardipine in humans: evidence for dominant presystemic elimination at the gut site. Eur J Clin Pharmacol 56:643–649
20. Sigusch H, Hippius M, Henschel L, Kaufmann K, Hoffmann A (1994) Influence of grapefruit juice on the pharmacokinetics of a slow release nifedipine formulation. Pharmazie 49:522–524
21. Bailey DG, Arnold JM, Strong HA, Munoz C, Spence JD (1993) Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. Clin Pharmacol Ther 54:589–594
22. Takanaga H, Ohnishi A, Murakami H, Matsuo H, Higuchi S, Urae A, Irie S, Furuie H, Matsukuma K, Kimura M, Kawano K, Orii Y, Tanaka T, Sawada Y (2000) Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. Clin Pharmacol Ther 67:201–214
23. Fuhr U, Muller Peltzer H, Kern R, Lopez Rojas P, Junemann M, Harder S, Staib AH (2002) Effects of grapefruit juice and smoking on verapamil concentrations in steady state. Eur J Clin Pharmacol 58:45–53
24. Zaidenstein R, Dishi V, Gips M, Soback S, Cohen N, Weissgarten J, Blatt A, Golik A (1998) The effect of grapefruit juice on the pharmacokinetics of orally administered verapamil. Eur J Clin Pharmacol 54:337–340
25. Sigusch H, Henschel L, Kraul H, Merkel U, Hoffmann A (1994) Lack of effect of grapefruit juice on diltiazem bioavailability in normal subjects. Pharmazie 49:675–679
26. Christensen H, Asberg A, Holmboe AB, Berg KJ (2002) Coadministration of grapefruit juice increases systemic exposure of diltiazem in healthy volunteers. Eur J Clin Pharmacol 58:515–520
27. Schwartz JB (1988) Effects of amlodipine on steady-state digoxin concentrations and renal digoxin clearance. J Cardiovasc Pharmacol 12:1–5
28. Rehnqvist N, Billing E, Moberg L, Lundman T, Olsson G (1987) Pharmacokinetics of felodipine and effect on digoxin plasma levels in patients with heart failure. Drugs 34[Suppl 3]:33–42
29. Dunselman PH, Scaf AH, Kuntze CE, Lie KI, Wesseling H (1988) Digoxin-felodipine interaction in patients with congestive heart failure. Eur J Clin Pharmacol 35:461–465
30. Debruyne D, Commeau P, Grollier G, Huret B, Scanu P, Moulin M (1989) Nicardipine does not significantly affect serum digoxin concentrations at the steady state of patients with congestive heart failure. Int J Clin Pharmacol Res 9:15–19
31. Belz GG, Doering W, Munkes R, Matthews J (1983) Interaction between digoxin and calcium antagonists and antiarrhythmic drugs. Clin Pharmacol Ther 33:410–417
32. Kirch W, Stenzel J, Dylewicz P, Hutt HJ, Santos SR, Ohnhaus EE (1986) Influence of nisoldipine on haemodynamic effects and plasma levels of digoxin. Br J Clin Pharmacol 22:155–159
33. Pedersen KE, Thayssen P, Klitgaard NA, Christiansen BD, Nielsen-Kudsk F (1983) Influence of verapamil on the inotropism and pharmacokinetics of digoxin. Eur J Clin Pharmacol 25:199–206
34. Rameis H, Magometschnigg D, Ganzinger U (1984) The diltiazem-digoxin interaction. Clin Pharmacol Ther 36:183–189
35. Elkayam U, Parikh K, Torkan B, Weber L, Cohen JL, Rahimtoola SH (1985) Effect of diltiazem on renal clearance and serum concentration of digoxin in patients with cardiac disease. Am J Cardiol 55:1393–1395
36. Guidelines for Package Inserts for Prescription Drugs, Notification No. 606 of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (April 25, 1997)
37. Guidelines for Package Inserts for Prescription Drugs, Notification No. 59 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (April 25, 1997)
38. Guidelines for Precautions for Prescription Drugs, Notification No. 607 of the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (April 25, 1997)

Bull. Natl. Inst. Health Sci., 123, 12-18 (2005) **Originals**

日本の医薬品添付文書におけるCYPに関する情報の解析研究

平田睦子[#]，齋藤充生，浦野　勉，三宅真二，長谷川隆一

Improvement of Package Insert CYP Information for Prescription Drugs Marketed in Japan

Mutsuko Hirata-Koizumi, Mitsuo Saito, Tsutomu Urano, Shinji Miyake and Ryuichi Hasegawa

In clinical practice, one drug is frequently used in combination with one or more other drugs, rather than as a sole regimen, and therefore healthcare providers need to carefully consider drug interactions. As mechanisms of drug interactions, metabolic enzymes of drugs are seen as one of the most likely interactive sites, where a majority of drugs are metabolized by cytochrome P450 (CYP). For this reason, providing appropriate information on CYP in package inserts is of grave importance. In fact, the package insert is the primary tool for supplying information on drugs to healthcare providers. The present study was designed to determine how many package inserts of prescription drugs marketed in Japan were providing CYP information. We searched the April 2003 version of "Drugs in Japan DB," which listed 2,022 prescription drugs, and found that only 239 package inserts (11.8%) mentioned CYP information and that only 194 (9.6%) specified CYP isozymes. To assess the improvement of package inserts, we searched "Drugs in Japan DB" from the January 2000 version to the April 2003 version. We found that CYP information had increased year by year (eg, 7.8-11.8% annually). For newly approved drugs, an analysis of the relationship between approval year and CYP information in package inserts (April 2003 version) revealed that recently approved drugs had more CYP information (eg, 45.5-51.3% of drugs in 1999-2002, compared to 6.8-26.1% in 1991-1996). A search for regulatory review documents for new drugs approved from 1999 to 2002 suggested that this recent improvement could be related to the increased number of studies identifying CYP isozymes involved in the metabolism or interaction with other drugs. Another reason for the recent improvement may be the fact that the guideline for package inserts for prescription drugs was revised in 1997, and the guidelines for drug interaction and pharmacokinetic studies were published between 1997 and 1999.

Key Words: package insert, CYP information, CYP isozyme, prescription drug

(Received May 31, 2005)

緒　言

医薬品は臨床において単独で投与されるよりむしろ併用して用いられることが多く，この様な場合，併用した医薬品間の相互作用に十分に注意を払う必要がある．医療従事者が医薬品の有効性および安全性に関わる情報を入手するための第一の手段は添付文書であり，医薬品適正使用の観点から，相互作用に関する適切な情報が添付文書に記載されていることが必要である．

医薬品の相互作用は，その機序により薬力学的相互作用と薬物動態学的相互作用に分けられるが，実際に報告されている相互作用のうち約60％は後者であり，また，その約65％は代謝部位で起きると考えられている[1]．近年，代謝部位における相互作用が要因で起きた副作用により，いくつかの医薬品が販売中止となっている．米国および欧州諸国で販売されていたカルシウム拮抗剤mibefradilは，強力なチトクロームP450（CYP）3A4阻害作用を持つことが知られており，承認後約1年の間に多くの医薬品との著しい相互作用が報告されたことから，1998年に販売中止となった[2,3]．また，日本を始め，世界各国で消化管機能調整薬として広く使用されていたcisaprideは，その重篤な副作用（QT延長および致死的心室性不整脈）から，2000年に販売中止もしくは停止となった[3]．報告されたcisaprideの副作用のうち，多くがCYPを阻害する医薬品もしくはQT間隔を延長する薬剤を併用したために生じたと考えられている[4]．

[#]To whom correspondence should be addressed: Mutsuko Hirata-Koizumi; Kamiyoga-1-18-1, Setagaya-ku, Tokyo 158-8501, Japan; Tel: 03-3700-1141 ext.561; Fax: 03-3700-9788; E-mail: mkoizumi@nihs.go.jp

この様に代謝部位における相互作用は，時に重篤な結果を招くことがあり，こうした相互作用による被害を防ぐためには，それぞれの医薬品の代謝および相互作用に関わる代謝酵素に関する情報が必須と考えられる．医薬品の代謝に関しては，CYPが重要な役割を果たしており，代謝部位における相互作用のうち9割以上がCYPを介したものと考えられている[1]．CYPについては，近年，その分子種を含め，多くの研究成果が公表されてきており，その研究情報が適正に添付文書に反映されていることが必要と考えられる．しかしながら，全医薬品添付文書にわたるCYPの記載状況の調査は現在までに行われていない．そこで，本研究では，日本の医薬品添付文書におけるCYP関連情報の提供状況を調査した．

研究方法

各調査で対象とした医薬品，医薬品数およびその情報源をTable1に示す．

最初に，2003年4月版日本医薬品集DB[5]を用いて，日本で販売されている医療用医薬品の添付文書におけるCYP関連情報の記載状況の調査を行った．次に2000年1月版，2001年4月版，2002年10月版の日本医薬品集DB[6~8]を用いて，CYP関連情報の記載状況の年次ごとの変化を調査した．関連情報として抱合および薬剤トランスポーターに関連した情報の記載状況についても同様の調査を行った．

さらに，1991年から2000年までの各年に承認された新有効成分含有医薬品名を医薬品製造指針[9]から，2001年および2002年に承認された新有効成分含有医薬品名を医薬品副作用被害救済・研究振興調査機構（現在の医薬品医療機器総合機構）の「医薬品情報提供ホームページ」[10]から入手し，日本医薬品集DB（2003年4月版）[5]を用いて，医薬品の承認取得年と添付文書中のCYP関連情報の記載状況との関連性を調査した．

最後に，添付文書に掲載されているCYP関連情報の情報源として，承認申請時に代謝および他剤との相互作用に関与するCYP分子種の特定を目的とした検討がどの程度行われているのか，また，その検討結果がどの程度添付文書に反映されているのか調査を行った．調査対象は，「医薬品情報提供ホームページ」[10]より承認審査報告書の入手が可能な1999年9月から2002年までに承認された新有効成分含有医薬品の中で日本医薬品集DB（2003年4月版）[5]に掲載されている医薬品とし，承認審査報告書におけるヒトの肝ミクロソームもしくはヒトCYP発現系を用いた試験の報告の有無を調べた．添付文書への反映状況については日本医薬品集DB（2003年4月版）[5]を用いて調査した．

研究結果

1．医薬品添付文書におけるCYP関連情報の記載状況

CYPについては，添付文書中では“チトクロームP450”，“チトクロームP-450”，“薬物代謝酵素CYP○○○”など様々な用語が用いられていた．そこで，本研究では，“CYP”，“P450”，“P-450”または“チトクローム”が添付文書中に記載されている医薬品を“CYP関連情報の記載がある医薬品”とし，調査を進めた．

その結果，239種の医薬品（11.8％）の添付文書中にCYP関連情報の記載が認められた．一方，194種の医薬品（9.6％）の添付文書中にCYP分子種が記載されていたが，添付文書中には，“主要代謝物の生成にはCYP○○○の関与は認められなかった”，“本剤はCYP○○○を阻害／誘導しない”，など，CYPの関与を否定する記載がみられたため，代謝および他剤との相互作用に関与するCYP分子種（関与のあるCYP分子種）についての記載のみに焦点を絞って再調査を行った．その結果をFig.1に示す．添付文書中に関与のあるCYP分子種の記載がみられた医薬品は188種（9.3％）であった．添付

Table.1　各調査で対象とした医薬品および情報源

対象医薬品	対象医薬品数	情報源
添付文書におけるCYPおよびその他の関連情報の記載状況		
日本で販売されている医療用医薬品（2003年4月現在）	2022	2003年4月版DB[5]
添付文書におけるCYPおよびその他の関連情報の記載状況の年次変化		
日本で販売されている医療用医薬品（2000年1月現在）	2044	2000年1月版DB[6]
日本で販売されている医療用医薬品（2001年4月現在）	2039	2001年4月版DB[7]
日本で販売されている医療用医薬品（2002年10月現在）	2021	2002年10月版DB[8]
医薬品の承認取得年と添付文書におけるCYP関連情報記載状況との関連性		
1991年から2002年までに日本で承認された新有効成分含有医薬品	347	医薬品製造指針[9] 医薬品情報提供ホームページ[10] 2003年4月版DB[5]
新薬承認審査報告書におけるCYP分子種の特定を目的とした試験の実施状況		
1999年9月から2002年までに日本で承認された新有効成分含有医薬品	95	医薬品情報提供ホームページ[10] 2003年4月版DB[5]

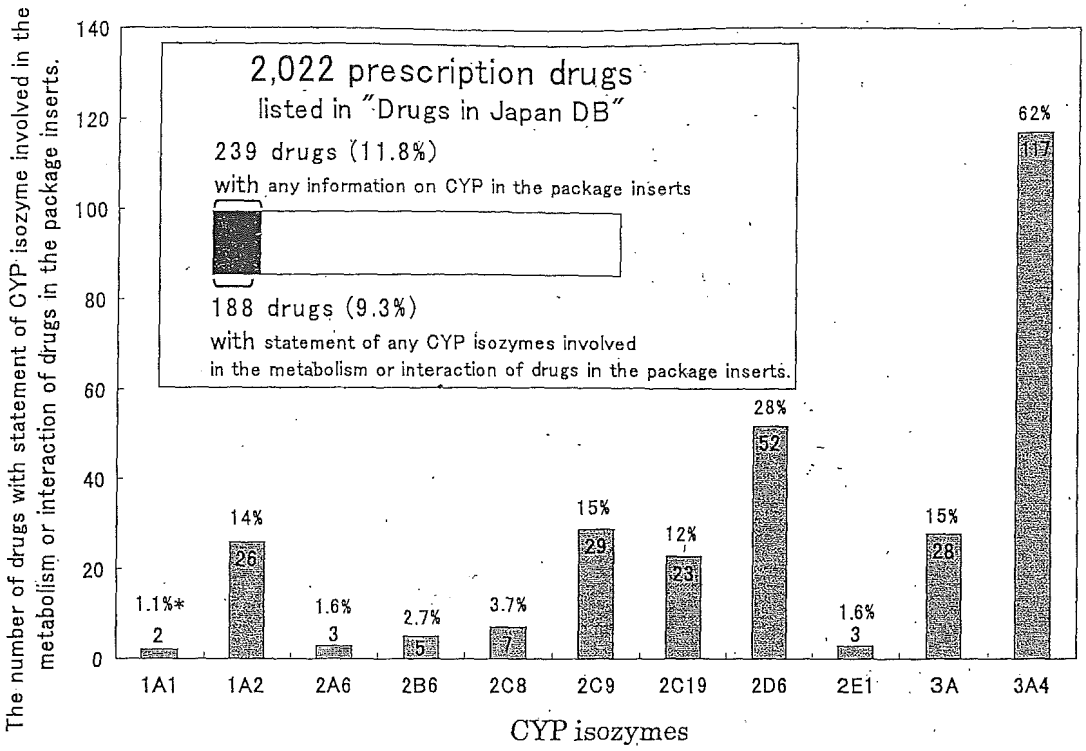

Fig.1 The number of drugs with statement of CYP isozymes involved in the metabolism or interaction with other drugs in the package inserts, with respect to each of the isozymes.

The April 2003 version of "Drugs in Japan DB" was searched to count the number of drugs with statement of each CYP isozyme, by which the drugs are metabolized or at which the drugs interact with other drugs. As the rest of CYP isozymes shown in this figure, CYP1A (the number of drugs: 1), CYP2B (1), CYP2C (2), CYP2C18 (2), CYP3A5 (1) and CYP24 (1) were also mentioned in package inserts.

* : Percentage to 188 drugs with statement of any of the CYP isozymes involved in the metabolism or interaction with other drugs in the package inserts

文書中に関与がある旨が最も多く記載されていたCYP分子種はCYP3A4（117種，添付文書中に関与のあるCYP分子種が記載されている医薬品188種中の62％）で，次いで，CYP2D6（52種，28％），CYP2C9（29種，15％），CYP1A2（26種，14％），CYP2C19（23種，12％）の記載が多く認められた．

2. 医薬品添付文書におけるCYP関連情報の記載状況の年次変化（Fig.2）

添付文書中にCYPに関連した記載，またCYP分子種の記載がある医薬品数は年次ごとに増加しており，2000年から2003年の約3年間で2倍近くとなっていた．主なCYP分子種，CYP3A4，CYP2D6，CYP2C9，CYP1A2，CYP2C19の記載状況の年次推移を調査した結果，添付文書中に各分子種が記載されている医薬品数はそれぞれ約3年間で2から3倍増加したが，分子種間での違いはみられなかった．

3. 医薬品添付文書におけるその他関連情報の記載状況およびその年次変化

添付文書中に，“抱合”の記載がみられた医薬品は265種あり，特に“グルクロン酸抱合”（176種）および“硫酸抱合”（29種）の記載が多く認められた．一方，添付文書中に“トランスポーター”の記載が認められた医薬品は3種のみであり，P-糖タンパク質に関しては7種の医薬品の添付文書で記載がみられた．

2000年1月版DB[6]を用いて調査した結果，255種の医薬品（12.5％）の添付文書中に“抱合”の記載，167種（8.2％）の医薬品の添付文書中に“グルクロン酸抱合”の記載が認められ，この約3年間で抱合に関する記載状況はほとんど変化していなかった．P-糖タンパク質を含む薬剤トランスポーターに関する情報については，2000年1月版DB[6]を用いた調査では，添付文書中に全く記載がみられなかったので，その後，初めて記載が行われたことになる．

4. 医薬品の承認取得年と添付文書におけるCYP関連情報記載状況との関連性（Fig.3）

CYP関連情報の記載は，1991-96年に承認されたものでは7－26％，1999－2002年のものでは46－51％の医薬品の添付文書中にみられ，特に1996－1999年の間に大幅な増加が認められた．

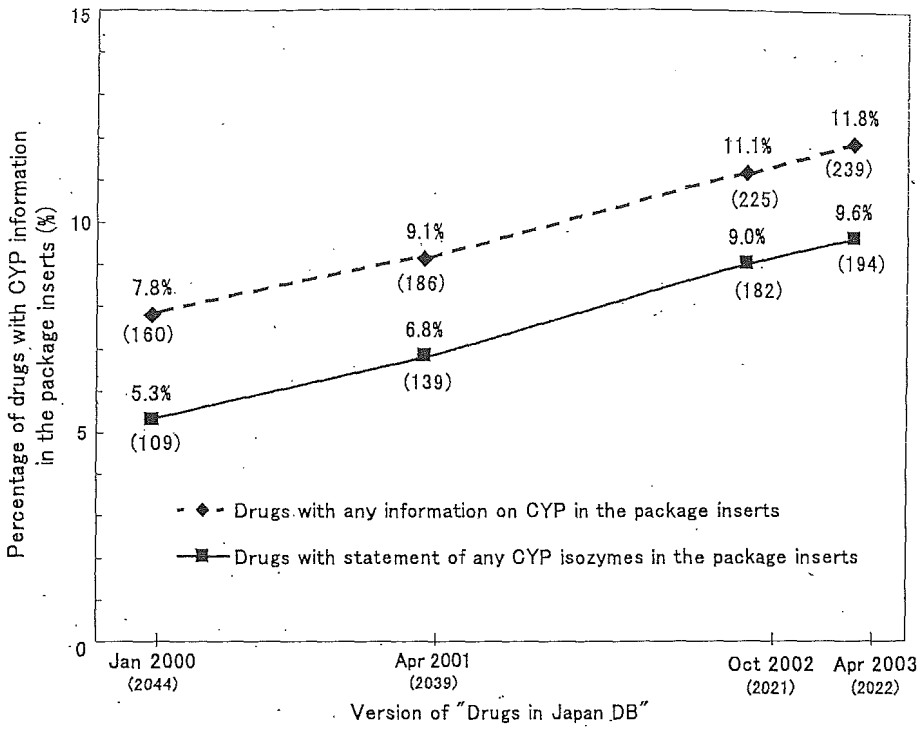

Fig.2 Linear increment in the ratio of drugs with CYP information in the package inserts from 2000 to 2003.
The January 2000 version, the April 2001 version, the October 2002 version and the April 2003 version of "Drugs in Japan in DB" were searched to count the number of drugs with information on CYP or CYP isozymes in the package inserts. The parenthesis inside the figure indicates the number of drugs with any information on CYP or CYP isozymes in the package inserts. The parenthesis below the horizontal axis indicates the number of all drugs listed in each version of "Drugs in Japan in DB".

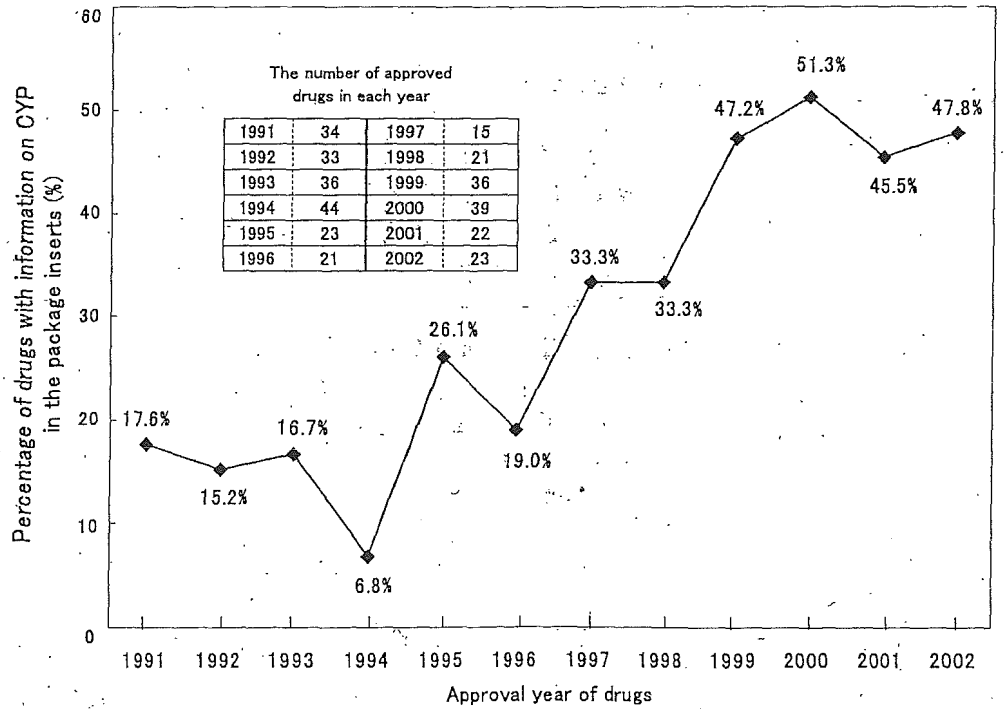

Fig.3 The number of annually approved drugs and change in the ratio of drugs with CYP information in the package inserts by the approval year.
For drugs with new active ingredients approved from 1991 to 2002, the package inserts were searched for any information on CYP, using the April 2003 version of "Drugs in Japan DB". The number of drugs with any information on CYP in the package inserts was counted by the approval year, and the percentage to all drugs approved each year was calculated.

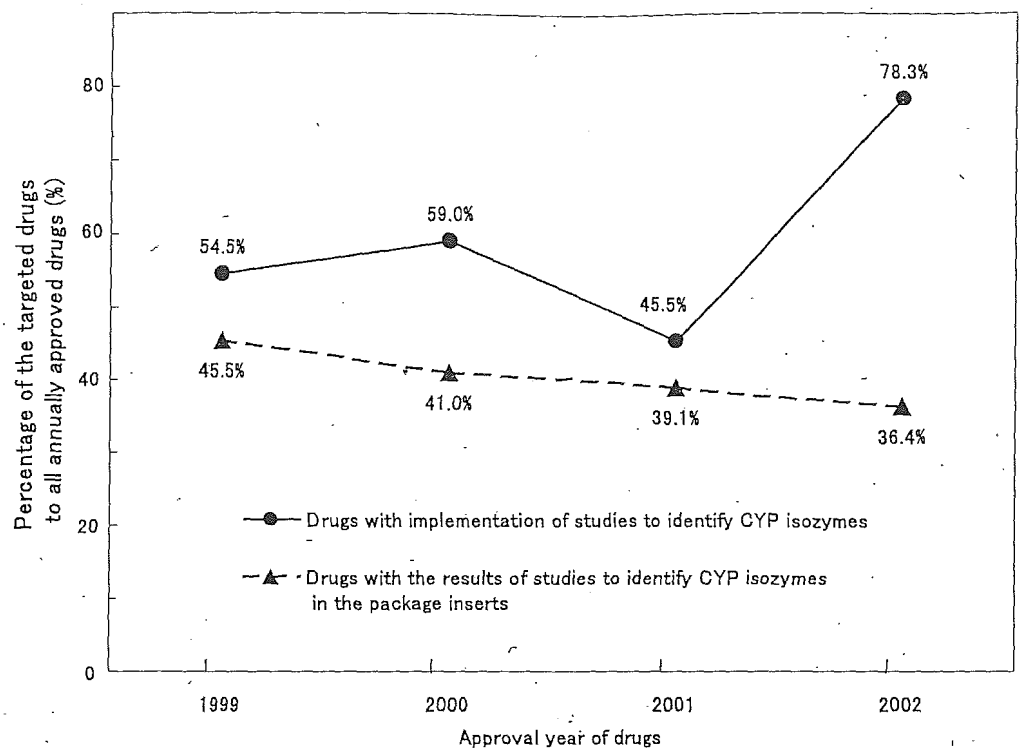

Fig.4 The implementation of studies to identify CYP isozymes for new drug application from 1999 to 2002 and reflection of the results in package inserts

Regulatory review documents for drugs with new active ingredients approved from September 1999 to 2002 were searched for studies identifying CYP isozymes involved in the metabolism and interaction with other drugs. The number of drugs, on which the study was conducted for new drug application, and having the results in their package inserts of the April 2003 version of "Drugs in Japan DB", was counted by the approval year, and the percentage to all drugs approved each year was calculated.

5. 新薬承認審査報告書におけるCYP分子種の特定を目的とした試験の実施状況

CYP分子種の特定を目的とした試験（CYP特定試験）の実施率は1999年から2001年までは45－60％程度であり，大きな変化は認められなったものの，2002年には著しい増加がみられた（Fig.4）．一方，CYP特定試験の結果が添付文書に記載されている医薬品の割合には低下傾向が認められた（Fig.4）．承認時にCYP特定試験が実施されていたにもかかわらず，その情報が添付文書に記載されていない医薬品が19種（CYP特定試験が実施された医薬品: 56種）あったが，そのうち13種の医薬品の承認審査報告書には代謝および相互作用へのCYPの関与を否定する結果が報告されていた．

考 察

日本では，1993年のソリブジン事件を機に，添付文書における医薬品安全性情報，特に相互作用に関する情報のあり方が重要視されるようになってきた．その後，添付文書の見直しに関する様々な検討がなされ，1997年4月に医療用医薬品添付文書の記載要領が改正された[11~13]．この新記載要領では，相互作用を従来の記述方式から，より分かり易い表形式として記載することとされた．さらに，特に重要な相互作用（結果として致死的または極めて重篤な副作用が発現する場合など）については，「相互作用」の項だけではなく，「警告」，「禁忌」，「重要な基本的注意」の項にも記載されるようになり，更なる注意喚起を行うこととなった．現在は，この記載要領に従って添付文書が作成されている．しかし，この記載要領では，相互作用の一覧表中に機序について記載することとされたものの，CYPを含む薬物代謝酵素に関連した情報の記載については具体的に言及されていない．

本研究の結果，日本で販売されている医療用医薬品のうち，約12％の医薬品の添付文書中にCYP関連情報が記載されていることが明らかになった．現在臨床で用いられている薬の80％以上がCYPにより代謝されていると言われていること[1]から考えると，代謝部位における相互作用がほとんど問題とならない皮膚塗布剤，貼付剤等の外用薬（約20％）を除外しても，添付文書におけるCYP関連情報の記載量は少なく，添付文書中のCYP関連情報はさらに充実されるべきものと考えられた．

2000年から2003年の日本医薬品集DBを用いた調査で

は，添付文書中のCYP関連情報は年次毎に充実してきていることが明らかとなった（Fig.2）．この結果は，ヒト組織を用いた研究体制の整備[14]を含む，CYP分子種に関する研究の進展に伴うものと考えられた．一方，承認取得年ごとの調査では，1996年から1999年までの増加が著しかった（Fig.3）が，これは1997年の医療用医薬品の添付文書記載要領改訂に加え，1997年の医薬品医療機器審査センター（現在の医薬品医療機器総合機構）の発足に伴う審査体制の充実，また，1998年の非臨床薬物動態ガイドラインの通知[15]をはじめとする国内外での関連ガイドラインの整備[16~18]により，試験方法や考慮すべき事項が明確化されたことによる影響と考えられた．

新薬承認審査報告書を調査した結果，1999年以降に承認された医薬品の45％以上については，承認時にCYP特定試験を実施していることが明らかとなった．従って，添付文書におけるCYP関連情報の記載率の増加（Fig.3）には，CYP特定試験実施率の増加が関与していると考えられた．一方，CYP特定試験実施率は2002年に増加を示したものの，CYP特定試験結果が添付文書に反映されている医薬品の割合は1999年から2002年にかけて低下傾向を示した（Fig.4）．CYP特定試験の結果を解析したところ，代謝および他剤との相互作用へのCYPの関与を否定する結果が得られたnegative dataについては，添付文書に反映されない傾向があり，このことがCYP特定試験結果の添付文書への反映率の低下の主な要因となっていると考えられた．しかし，この様なCYPの関与や他剤との相互作用を否定する情報は併用薬との相互作用を考慮した上での医薬品の選択を容易にすることから，これらの情報も添付文書に明記される必要があると考えられた．

最近，医薬品の吸収，体内分布および排泄に重要な役割を果たしている薬剤トランスポーターが，医薬品相互作用の新たなメカニズムとして注目されるようになってきた．P-糖タンパク質は，肝細胞，小腸上皮細胞，近位尿細管上皮細胞，血液脳関門，血液胎盤関門等に発現し，医薬品の排出方向への輸送を担う薬剤トランスポーターである[19]．P-糖タンパク質を介した相互作用に関しては多くの報告があり，よく知られている例としては，verapamilやquinidine等の心臓作用薬の併用によるdigoxinの血中濃度の増加がある[20~23]．一方で，P-糖タンパク質はその基質，阻害剤，誘導剤がCYPと共通しているため[19]，今までCYPを介するとされてきた相互作用へのP-糖タンパク質の寄与が示唆されている．しかし，現時点では，添付文書にP-糖タンパク質を含む薬剤トランスポーターに関する情報はほとんど認められなかった．薬剤トランスポーターに関する情報はCYPと同様に医薬品適正使用の観点から重要な情報と考えられることから，薬剤トランスポーターが関与する相互作用について今後の更なる研究の実施およびそれらの情報の添付文書へ反映が望まれる．

最後に，本研究は，医薬品の相互作用に関する研究の第一歩として，日本の添付文書におけるCYP関連情報の記載状況の全体像を調査したものである．本研究の成果に基づき，スタチン系薬剤およびカルシウム拮抗剤の薬物動態学的相互作用について，文献情報を収集・整理・解析し，日本と米国および欧州等の添付文書における情報提供状況の比較・解析を行った[24,25]．今後も，さらに，医薬品相互作用に関するより適切な情報提供のあり方についての研究を進める予定である．

結　論

本研究では，医薬品の相互作用において重要な役割を果たしているCYPに関する情報が医療用医薬品の添付文書にどの程度記載されているのかを調査した．その結果，添付文書におけるCYP関連情報は，年次毎に充実してきており，現時点（2003年4月）では，約12％の添付文書中にCYP関連情報が，約10％の添付文書中にCYP分子種が記載されていることが明らかになった．

参考文献

1) 加藤隆一：臨床薬物動態学－臨床薬理・薬物療法の基礎として－，改訂第3版，南江堂，東京（2003）
2) Po, A.L. and Zhang, W.Y.: *Lancet*, **351**, 1829-1830 (1998)
3) WHO: "Pharmaceuticals: Restriction in use and availability", World Health Organization, Geneva, Switzerland (2001)
4) Wysowski, D.K., Corken, A., Gallo-Torres, H., Talarico, L. and Rodriguez, E.M.: *Am. J. Gastroenterol.*, **96**, 1698-1703 (2001)
5) 日本医薬品情報センター，じほう："日本医薬品集DB 2003年4月版"，じほう（2003）
6) 日本医薬品情報センター，じほう："日本医薬品集DB 2000年1月版"，じほう（2000）
7) 日本医薬品情報センター，じほう："日本医薬品集DB 2001年4月版"，じほう（2001）
8) 日本医薬品情報センター，じほう："日本医薬品集DB 2002年10月版"，じほう（2002）
9) 薬事審査研究会："医薬品製造指針 2001"，じほう（2001）
10) 医薬品医療機器総合機構：医薬品医療機器情報提供ホームページ（http://www.info.pmda.go.jp/）
11) 厚生省：薬務局長通知，「医療用医薬品添付文書の記載要領について」，平成9年4月25日薬発第606号
12) 厚生省：薬務局長通知，「医療用医薬品の使用上の注意記載要領について」，平成9年4月25日薬発第

607号
13) 厚生省：薬務局安全課長通知，「医療用医薬品添付文書の記載要領について」，平成9年4月25日薬安第59号
14) 厚生省：「手術等で摘出されたヒト組織を用いた研究開発の在り方について（答申）」，平成10年12月16日厚科審第13号
15) 厚生省：医薬安全局審査管理課長通知，「非臨床薬物動態試験ガイドラインについて」，平成10年6月26日医薬審第496号
16) FDA: Guidance for Industry: Drug Metabolism / Drug Interaction Studies in the Drug Development Process: Studies in Vitro (Apr 1997)
17) FDA: Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies-Study Design, Data Analysis, and Recommendations for Dosing and Labeling (Nov 1999)
18) EMEA: Note for Guidance on the Investigation of Drug Interactions (Dec 1997)
19) Lin, J.H. and Yamazaki, M.: *Clin. Pharmacokinet.*, **42**, 59-98 (2003)
20) Bussey, H.I.: Am. Heart J., 104, 289-302 (1982)
21) Pedersen, K.E.: *Acta. Med. Scand. Suppl.*, **697**, 1-40 (1985)
22) Mordel, A., Halkin, H., Zulty, L., Almog, S. and Ezra, D.: *Clin. Pharmacol. Ther.*, **53**, 457-462 (1993)
23) Verschraagen, M., Koks, C.H., Schellens, J.H. and Beijnen, J.H.: *Pharmacol. Res.*, **40**, 301-306 (1999)
24) Saito, M., Hirata-Koizumi, M., Urano, T., Miyake, S. and Hasegawa, R.: *J. Clin. Pharm. Therap.*, **30**, 21-37 (2005)
25) Saito, M., Hirata-Koizumi, M., Miyake, S. and Hasegawa, R.: *Eur. J. Clin. Pharm.*, **61**, 531-536 (2005)

Bull. Natl. Inst. Health Sci., 123, 37-40 (2005)

シクロスポリンによるスタチン系薬剤の著しい血中濃度増加作用とその機序及び添付文書における情報の解析

平田睦子[#]，齋藤充生，三宅真二，長谷川隆一

The Incremental Effect and Mechanism of Cyclosporine on Blood Concentration of Statins and Statin Package Insert Information in Japan

Mutsuko Hirata-Koizumi[#], Mitsuo Saito,
Shinji Miyake, Ryuichi Hasegawa

Cyclosporine is an indispensable immunosuppressant used in organ transplant patients, who frequently manifest hyperlipidemia. Statins, which are cholesterol-lowering agents, are often combined with cyclosporine in the treatment of hyperlipidemia of organ transplant patients. Since cyclosporine is a substrate and inhibitor of CYP3A4, researchers suspect that the immunosuppressant inhibits CYP3A4-mediated metabolism of statins, leading to an increase in statin plasma concentration and infrequently resulting in rhabdomyolysis. However, a number of clinical trials have shown cyclosporine to increase the plasma concentration of all developed statins, including those not metabolized by CYP3A4. Furthemore, recent mechanistic studies have shown organic anion transporting peptides (OATP) C to mediate the uptake of some statins and cyclosporine has been shown to inhibit the uptake via OATP-C in cultured cells. Therefore, the inhibition of hepatic uptake of statins is considered to be one of the mechanisms by which cyclosporine incrementally increases statin blood concentration. However, most current Japanese package inserts of statins give no information on change in pharmacokinetic parameters such as AUC and Cmax in the combined medication with cyclosporine. Furthermore, in the Japanese package inserts, it is either stated that cyclosporine inhibits CYP3A4-mediated metabolism or no comment is made on the mechanism. The package insert should properly provide available quantitative information on the change of pharmacokinetic parameters and the probable mechanism of action.

Key Words: cyclosporine, statin, drug-drug interaction, CYP3A4, rhabdomyolysis

(Received May 31, 2005)

はじめに

Cyclosporineは臓器移植に不可欠な医薬品（免疫抑制剤）の一つであり，多くの臓器移植患者に使用されている．臓器移植により高脂血症が誘発されることが多いため，cyclosporineはスタチン系薬剤と併用して投与される場合が多い．スタチン系薬剤はコレステロール生合成の律速酵素であるHMG-CoA還元酵素を特異的に阻害し，血中のコレステロール濃度を減少させる薬剤であるが，その重篤な副作用としてまれに横紋筋融解症が発現し，時として死に至る．一方，cyclosporineとスタチン系薬剤の併用投与が原因と推定される横紋筋融解症の症例報告が多数あり[1~5]，これはcyclosporineがCYP3A4の基質であり，かつCYP3A4阻害作用を持つため，CYP3A4で代謝を受けるスタチン系薬剤の代謝が阻害されたことによると考えられていた．しかし，CYP3A4による代謝を受けないスタチン系薬剤についてもcyclosporineの併用により血中濃度の増加することが報告され，CYP3A4を介さない相互作用機序の存在が示唆されている．

Cyclosporineによるスタチン系薬剤の血中濃度増加の程度やその機序に関する情報を適切に提供することは，スタチン系薬剤の副作用を回避する上で非常に重要であると考えられる．そこで，本稿ではcyclosporineとスタチン系薬剤との臨床薬物動態学的相互作用並びにその作用機序に関する文献情報を収集・解析するとともに，日本で市販されているスタチン系薬剤の医薬品添付文書を点検し，添付文書による情報提供の現状を把握することとした．

[#]To whom correspondence should be addressed: Mutsuko Hirata-Koizumi; Kamiyoga-1-18-1, Setagaya-ku, Tokyo 158-8501, Japan; Tel: 03-3700-1141 ext.561; Fax: 03-3700-9788; E-mail: mkoizumi@nihs.go.jp

調査方法

Medlineを用いて，現在までに開発されたすべてのスタチン系薬剤とcyclosporineとの臨床薬物動態学的相互作用並びにそれらの作用機序に関する文献を検索し，総合的に解析した．また，独立行政法人医薬品医療機器総合機構のホームページ[6]から，現在日本において市販されているスタチン系薬剤の添付文書（先発企業作成分）を入手し，cyclosporineとの相互作用の機序等についての情報提供の現状を調査した．

調査結果及び考察

現在までに開発されたスタチン系薬剤にはatorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, pravastatin, pitavastatin, rosuvastatinがある．これら8種類のスタチン系薬剤のうち，日本ではlovastatinは承認されておらず，cerivastatinは1999年に承認されたものの，2001年には企業による自主的な市場撤退に至っている．

1. スタチン系薬剤の代謝及びcyclosporineの併用投与による血中濃度の増加

スタチン系薬剤の代謝に関わる酵素をTable.1に示した．Atorvastatin, simvastatin及びlovastatinはCYP3A4により代謝される．一方，fluvastatinはCYP2C9により，cerivastatinはCYP3A4とCYP2C8の両酵素により代謝され，pravastatin, pitavastatin及びrosuvastatinはCYPによってはほとんど代謝されない．

すべてのスタチン系薬剤について，cyclosporineの併用投与による血中濃度の変動に関する文献が報告されていた（Table.1）．これらは全て移植患者から得られたデータであるが，cyclosporine併用時のスタチン系薬剤のAUCはいずれも単独投与に比べて3倍以上に増加していた．CyclosporineにはCYP3A4阻害作用があるが，CYP3A4で代謝されるatorvastatin, simvastatinやlovastatinに対する特異性は全く見られていない．なお，Table1に含まれないデータとして，cyclosporineとの併用によりpravastatinのAUCが23倍に増加した報告があったが[23]，これは学会要旨としての報告であり，その後も，投与や分析方法を含めた詳細な試験条件及び結果の報告が無いため，数値の信頼性は低いと考えられる．

Table.1 Major metabolic enzymes, CYPs of statins and increase in AUC of statins in combination with cyclosporine in organ transplant patients

Name of statins	Metabolic enzymes[7-9]	Increase of AUC
Atorvastatin	CYP3A4	6[a] - 9 fold[10,11]
Simvastatin	CYP3A4	3 - 8 fold[12-14]
Lovastatin	CYP3A4	5 - 20 fold[15,16]
Fluvastatin	CYP2C9	3 fold[17,18]
Cerivastatin	CYP3A4 & CYP2C8	3 - 5 fold[19]
Pravastatin	[Not metabolized by CYPs]	5 - 12 fold[15,20]
Pitavastatin	CYP2C9 (slightly)	5 fold[21]
Rosuvastatin	[Not metabolized by CYPs]	7 fold[22]

a) HMG-CoA reductase activity was measured.

2. Cyclosporineによるスタチン系薬剤の血中濃度増加機序に関する研究

Smithら[24]は，雌のSDラットにsimvastatin, lovastatin及びpravastatinを投与すると用量依存的に筋症が発現し，さらに，cyclosporineの併用によりこの筋毒性が強く増強されることを示した．そこで，cyclosporine（10 mg/kg/day）とこれらのスタチン系薬剤を4週間併用投与し，筋組織中のHMG-CoA還元酵素阻害活性を測定した結果，cyclosporine併用によりsimvastatin（50 mg/kg/day）で1.5倍，lovastatin（100 mg/kg/day）で約13倍，pravastatin（100 mg/kg/day）で約3倍に増加した．しかし，ラット肝ミクロソームを用いて，lovastatin 100 μMの代謝速度を測定した結果，cyclosporine 10-200 μM存在下で代謝抑制は認められなかった．なお，臨床（安定した腎移植患者）において通常用量下でのcyclosporineの平均最高血中濃度は，724-979 ng/mL（0.60-0.81 μM）であったことが報告されている[25,26]．これらの結果から，cyclosporineによるスタチン系薬剤の血中濃度増加は代謝阻害ではなく，スタチン系薬剤の血中からの排泄阻害により起きると推測された．

その後，Hsiangら[27]はヒトOATP-C（Organic Anion Transporting Peptides-C：主に肝細胞の血液側膜に存在して，血液からの取り込みに関与する有機アニオントランスポータ）を組み込んだ293c18細胞を用いて，pravastatin（0.5 μM）の取り込みに対するスタチン系薬剤（50 μM）による阻害率を測定した結果，atorvastatin, simvastatin, lovastatin及びatorvastatinの2つの代謝物はほぼ100％，pravastatinは30％の抑制率を示した．さらに，Shitaraら[28]はヒト肝培養細胞およびOATP-Cを発現させたMDCKII細胞において，cyclosporineがcerivastatinの取り込みを抑制すること（Ki：0.2-0.7 μM）を示した．なお，cerivastatinの代謝に対するcyclosporineのIC_{50}は30 μM以上であった．最近行われたOATP-Cを発現させた卵母細胞を用いた研究においても，cyclosporineがrosuvastatinの取り込みを抑制すること（IC_{50}：2.2 μM）が示されている[22]．これらの結果から，cyclosporineによるスタチン系薬剤の血中濃度の増加には，OATP-Cによるスタチン系薬剤の肝細胞への取り込みが寄与していると考えられた．