lism of fexofenadine and celiprolol is negligible in humans[99] and the amounts of drug excreted in urine was reduced without decreasing renal clearance, grapefruit juice was considered to inhibit the absorption of these drugs.[27,28] A possible mechanism is inhibition of uptake via OATP (see section 1.3). Fexofenadine is known to be a substrate of OATP, but there is no relevant information with regard to celiprolol. Other mechanisms, such as changes in intraduodenal pH and formation of complexes between drugs and components of grapefruit juice, cannot be discounted.

Itraconazole, an antifungal agent, is metabolised by CYP3A4 to hydroxyitraconazole. Concomitant intake of double-strength grapefruit juice with itraconazole capsules caused decreases in the AUC values for both itraconazole and hydroxyitraconazole of approximately 50%, but the metabolic ratio (hydroxyitraconazole AUC vs itraconazole AUC) was not affected, suggesting that there was no influence on itraconazole metabolism.[83] The investigators proposed that a decrease in duodenal pH or delay in gastric emptying by grapefruit juice would result in decreased itraconazole absorption. Involvement of OATP is also likely, although there is no actual evidence of this. Contrary to the findings reported in the above-mentioned study,[83] a recent study conducted by Gubbins et al.[100] showed a slight but significant increase (1.2-fold) in itraconazole AUC with grapefruit juice. This study evaluated the interaction between an oral solution of itraconazole formulated in hydroxypropyl-β-cyclodextrin and a different grapefruit juice schedule (ingestion of 240mL of single-strength grapefruit juice three times daily for 2 days). The investigators noted the differences in volume, viscosity and caloric density of the grapefruit juice preparation compared with standard regimens and further studies are needed.

It should be taken into account that the decrease in AUC and/or C_{max} of group 3 drugs caused by grapefruit juice interaction may lessen their pharmacological effects. Particularly in the case of celiprolol, which is indicated for hypertension, great care would need to be taken because the decrease in AUC and C_{max} could lead to a sharp rise in blood pressure. Although grapefruit juice effects on the pharmacokinetics of amprenavir, etoposide and theophylline are small, caution should also be taken with use of these drugs because of their narrow therapeutic range.

2.3.1 Discussion

Although the variability (individual differences) in clinical studies listed in the tables is generally high, this is dependent on the drugs studied. Therefore, it should be noted that small changes in average AUC and C_{max} do not always translate into a negligible effect in all individuals; very high individual differences in the bioavailability of ciclosporin, for example, can be observed. When focusing on how any particular drug is affected by grapefruit juice, the variability in the original report should be checked to obtain a true clinical perspective. The potential for different responses in sensitive subpopulations is another important issue. For example, a grapefruit-felodipine interaction study in elderly individuals showed greater increases (AUC 2.9-fold, C_{max} 4.0-fold)[101] than those reported in clinical studies that have mostly involved healthy young volunteers. Thus, the elderly should be particularly cautioned about concomitant ingestion of grapefruit juice with drugs.

From a different point of view, Bailey[89] has suggested that there are potential beneficial effects with concomitant ingestion of grapefruit juice, such as enhanced drug efficacy. As autoinduction of CYPs is a concern for CYP-metabolised drug therapy, grapefruit juice could be useful in the maintenance of drug effectiveness. However, because grapefruit is a natural product and the ingredient and mechanism of action responsible for its effects are not yet fully understood, it is difficult to recommend grapefruit juice as a booster. Another possible countermeasure is the substitution of grapefruit juice sensitive agents (group 1 drugs) for grapefruit juice tolerant agents (group 2 drugs) in the same therapeutic classes.[102] However, it should be noted that each drug has different characteristics, such as absorption, distribution, metabolism and excretion.

3. Interactions Between Other Citrus Juices and Drugs

Recently, some reports have been published regarding interactions between citrus juices other than grapefruit juice and drugs.

3.1 Orange Juice (Sweet)

In the first clinical study of grapefruit juice and drug interaction,[2] it became clear that orange juice, in contrast, did not affect the pharmacokinetics of felodipine. Subsequently, orange juice was sometimes used as a negative control in studies of grapefruit juice-drug interactions. However, notable clinical results that might reverse this long-held stance have recently been reported. In one study, orange juice reduced the AUC and C_{max} of fexofenadine by up to 30%, an effect similar to that of grapefruit juice.[27] Orange juice also substantially reduced the C_{max}, AUC and urinary excretion of celiprolol by 89%, 83% and 77%, respectively.[103] An *in vitro* study showed that orange juice has a much stronger inhibitory effect on OATP than P-glycoprotein,[27] so it would be expected to inhibit OATP-mediated transport rather than P-glycoprotein function *in vivo*. Unexpectedly, apple juice, a non-citrus juice, was also reported to have the same effect on fexofenadine *in vivo* and OATP-mediated transport *in vitro*.[27]

3.2 Seville (Sour) Orange Juice

Seville (sour) orange is mainly used for confectionary products such as marmalade. Although its juice is not fit to drink because of its sour taste, several interaction studies with Seville (sour) orange juice have been conducted. The increase in the AUC of felodipine, a CYP3A4 substrate, with Seville (sour) orange juice is the same as that observed with diluted grapefruit juice; both juice preparations contained the same total concentrations of candidate causative ingredients bergamottin plus 6′,7′-dihydroxybergamottin.[104] A significant increase in the oral bioavailability of dextromethorphan with Seville (sour) orange juice has also been reported.[41] Because it has been reported that Seville orange juice decreases the enterocyte concentration of CYP3A4,[22] mechanism-based inhibition must be considered. The lack of interaction between Seville (sour) orange juice and ciclosporin[22] suggests that Seville orange juice does not inhibit intestinal P-glycoprotein function.

3.3 Other Citrus Juices

The juice of another citrus, the tangerine (a kind of Mandarin orange), has been reported to decrease the AUC of midazolam (an anxiolytic) by about 40% over the first 1.5 hours and to increase T_{max} 2-fold without effects on total AUC, C_{max} and the AUC ratio of the main metabolite to midazolam.[105] Tangerine juice might have some impact on the absorption process of midazolam.

Lime juice has demonstrated mechanism-based inhibition of CYP3A4 activity *in vitro*.[10] However, in a clinical study, 25% diluted lime juice containing the candidate causative ingredient bergamottin in the same amounts as grapefruit juice (see section 4.1.2), did not exert any significant effects on the pharmacokinetic parameters of felodipine.[10]

To our knowledge, there is no further information available on interactions between drugs and tangerine or lime juice.

3.4 Target Sites of Citrus-Drug Interaction in Enterocytes

Both P-glycoprotein and OATP as well as CYP3A4 are expressed in the liver and their involvement in drug disposition and exclusion has been reported.[106-108] However, the lack of interaction between grapefruit juice and intravenously administered drugs[1,6,14,15,17] suggests that hepatic enzymes and transporters are minimally, if at all, in-

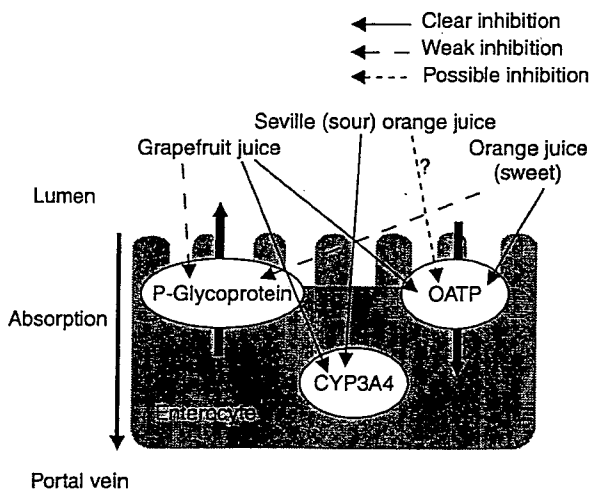

Fig. 1. The target sites in enterocytes of the small intestine for various citrus juices. **CYP3A4** = cytochrome P450 3A4; **OATP** = organic anion transporting polypeptide.

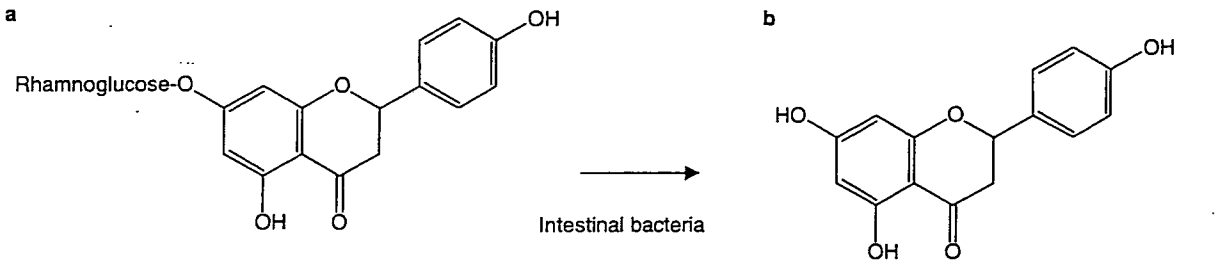

Fig. 2. Chemical structures of (a) naringin and (b) naringenin.

volved. Based on the findings mentioned in sections 1, 3.1 and 3.2 and the new model proposed by Dresser and Bailey,[29] we describe the target sites in small intestine enterocytes where various citrus juices exert their inhibitory actions (figure 1).

If drugs are substrates of CYP3A4, they will be partially metabolised in the intestine and their metabolites will appear in the portal vein. Drugs that are substrates of OATP will be absorbed into enterocytes with the aid of OATP and passed through to the portal vein. Drugs that are substrates of P-glycoprotein may be transported back into the small intestine.

Grapefruit juice inactivates CYP3A4 in a mechanism-based manner and inhibits the function of P-glycoprotein and OATP. It appears that orange juice has inhibitory effects on P-glycoprotein and OATP, but not on CYP3A4. The effects of grapefruit juice and orange juice on P-glycoprotein are likely to be weak. Seville (sour) orange juice is considered to inactivate CYP3A4 by a mechanism-based action, but not to inhibit the function of P-glycoprotein. Possible effects of Seville (sour) orange juice on OATP remain to be elucidated.

4. Causative Ingredients

Several hundred ingredients have been identified in grapefruit juice.[109] The composition of the juice varies widely, depending on the genetic background of the plant, environmental conditions during fruit growth, fruit maturity and fruit processing.[109,110] Although several studies have been conducted, definite conclusions as to causative ingredients cannot be drawn yet.

4.1 Candidate Ingredients for CYP3A4 Inhibition

Flavonoids and furanocoumarins, which are found in grapefruit juice and Seville (sour) orange juice but not in orange juice, have been proposed as causative ingredients of CYP3A4 inhibition by grapefruit juice.

4.1.1 Flavonoids

Naringin (naringenin glycoside) is the most prevalent flavonoid in grapefruit juice.[111] Although naringin is hydrolysed by intestinal bacteria to naringenin[112,113] (figure 2), which has CYP3A4 inhibitory activity *in vitro*,[3,4] clinical studies using commercially-available pure naringin have shown that it is not the major inhibitory ingredient of grapefruit juice.[114-116] Recently, naringenin was reported to cause competitive, but not mechanism-based, inhibition of CYP3A4 activity *in vitro*,[12] but such competitive inhibition is known to be not important for the clinical grapefruit juice-drug interaction.[89]

4.1.2 Furanocoumarins

The furanocoumarins exert mechanism-based inhibition of CYP3A4 *in vitro*,[9] but clinical studies using pure forms cannot be conducted because these have not yet been approved for human intake. Previously, although 6′,7′-dihydroxybergamottin (figure 3), one of the most abundant furanocoumarins, was proposed as an active ingredient in grapefruit juice, subsequent clinical studies using supernatant and particulate fractions obtained by means of centrifugation and filtration of grapefruit juice showed that 6′,7′-dihydroxybergamottin was not the major active ingredient.[117]

Information on bergamottin (figure 3), another major furanocoumarin, has been newly reported. Guo et al.[9] showed that bergamottin and some other

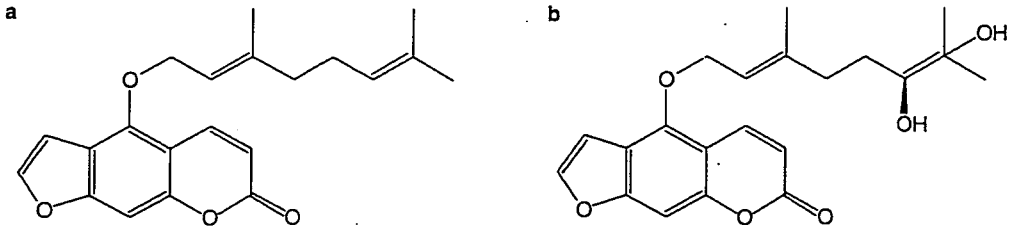

Fig. 3. Chemical structures of (**a**) bergamottin and (**b**) 6′,7′-dihydroxybergamottin.

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 nobiletin, 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.

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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

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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

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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).

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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

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

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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

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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]．

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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]

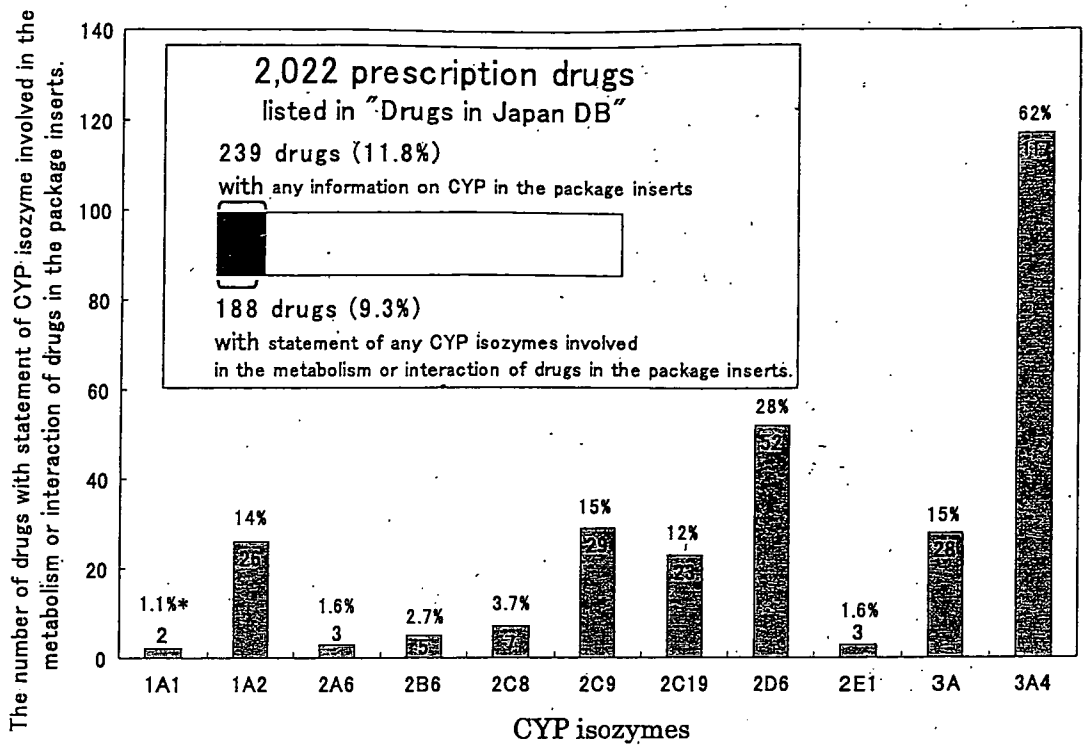

Fig.1 The number of drugs with statement of CYP isozymes involved in the metabolism or interaction with other drugs in the package inserts, with respect to each of the isozymes.
The April 2003 version of "Drugs in Japan DB" was searched to count the number of drugs with statement of each CYP isozyme, 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．

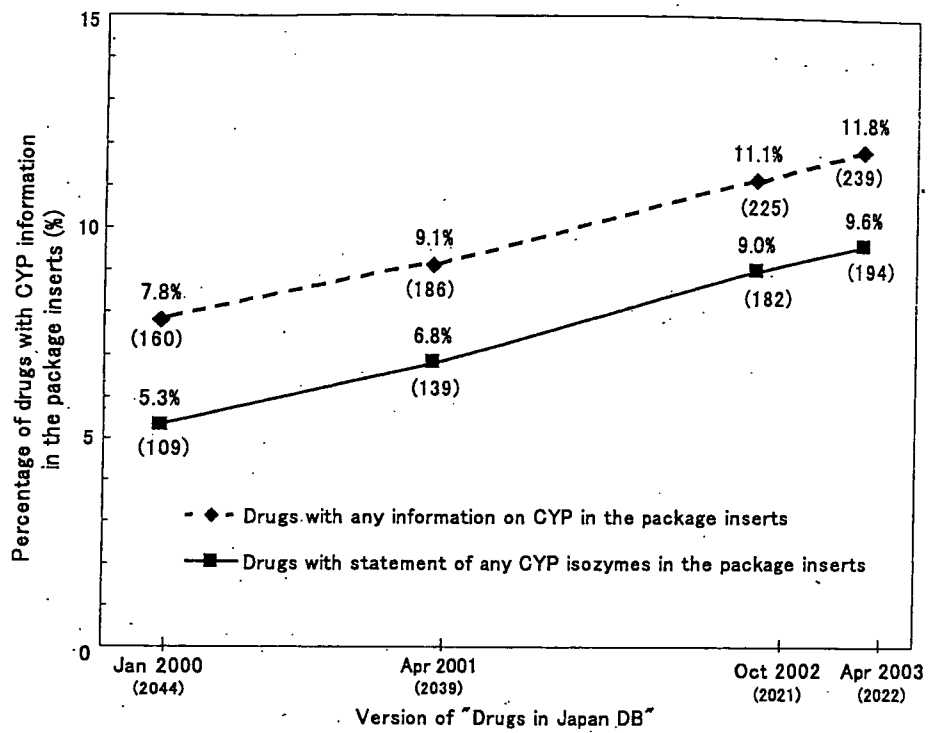

Fig.2 Linear increment in the ratio of drugs with CYP information in the package inserts from 2000 to 2003.
The January 2000 version, the April 2001 version, the October 2002 version and the April 2003 version of "Drugs in Japan in DB" were searched to count the number of drugs with information on CYP 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".

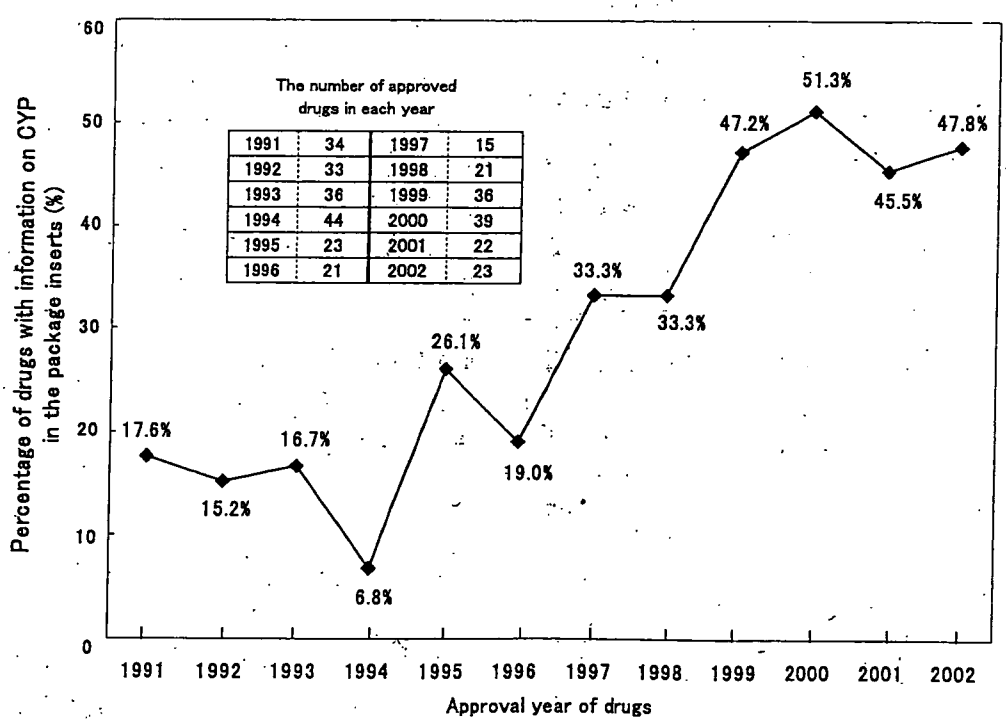

Fig.3 The number of annually approved drugs and change in the ratio of drugs with CYP information in the package inserts by the approval year.
For drugs with new active ingredients approved from 1991 to 2002, the package inserts were searched for any information on CYP, using the April 2003 version of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

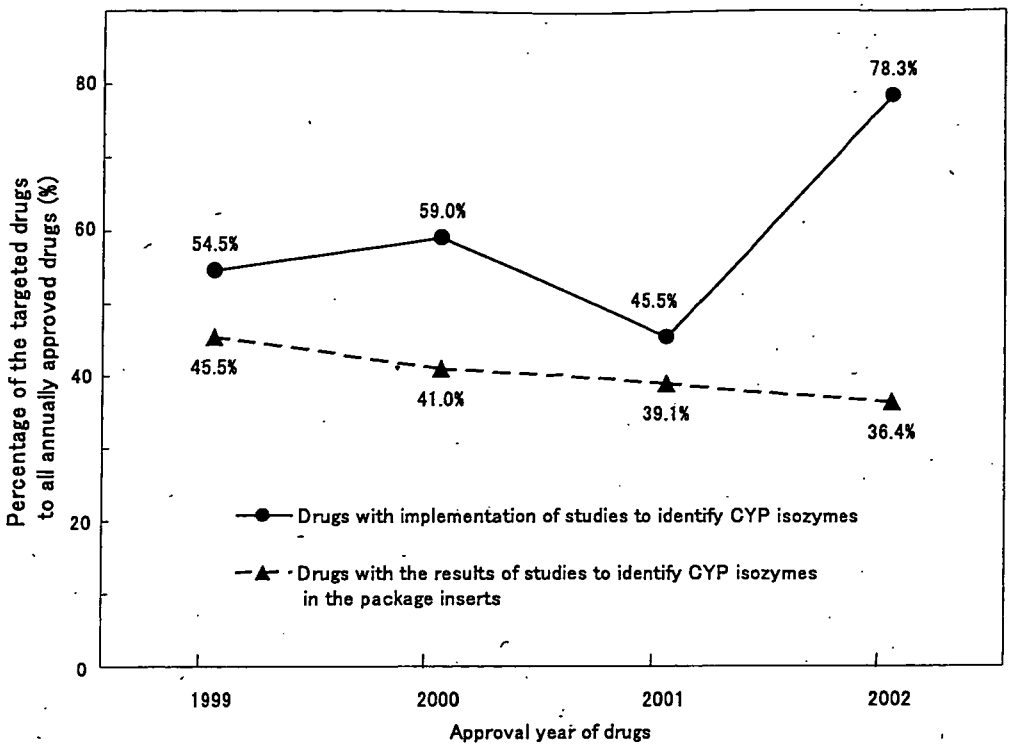

Fig.4 The implementation of studies to identify CYP isozymes for new drug application from 1999 to 2002 and reflection of the results in package inserts

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かったものの，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．

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