Table 7-1

フルバスタチンの添付文書：2003年6月改訂（第2版）：販売開始2003年6月

【使用上の注意】3.相互作用

代謝に関する記載なし。

［併用注意］（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
免疫抑制剤 シクロスポリン等 エリスロマイシン	急激な腎機能悪化を伴う横紋筋融解症があらわれるおそれがある。自覚症状（筋肉痛、脱力感）の発現、CK（CPK）上昇、血中及び尿中ミオグロビン上昇並びに血清クレアチニン上昇等の腎機能の悪化を認めた場合は直ちに投与を中止すること。	危険因子：腎障害患者
ジゴキシン	ジゴキシンのAUCに変化は認められなかったが、最高血中濃度が上昇したとの報告があるので、観察を十分に行うこと。	機序は解明されていない。

【薬物動態】2.代謝

フルバスタチンはヒト肝ミクロソームにより水酸化体及び脱イソプロピル化体へと代謝され、水酸化及び脱イソプロピル化には主としてCYP2C9が関与している。

Table 7-2

フルバスタチンの添付文書改訂案

【使用上の注意】3.相互作用

本剤は，主に肝代謝酵素チトクロームCYP2C9により代謝される。

［併用注意］（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
免疫抑制剤 シクロスポリン等 ~~エリスロマイシン~~	急激な腎機能悪化を伴う横紋筋融解症があらわれるおそれがある。自覚症状（筋肉痛、脱力感）の発現、CK（CPK）上昇、血中及び尿中ミオグロビン上昇並びに血清クレアチニン上昇等の腎機能の悪化を認めた場合は直ちに投与を中止すること。	シクロスポリンが本剤の肝への取り込みを抑制し、血中濃度の増加すること(AUC: 3-3.3倍)が報告されている。危険因子：腎障害患者
フルコナゾール		肝CYP2C9の阻害により，血中濃度の増加すること(AUC: 1.8倍)が報告されている。危険因子：腎障害患者
ジゴキシン	ジゴキシンのAUCに変化は認められなかったが、最高血中濃度が上昇したとの報告があるので、観察を十分に行うこと。	機序は解明されていない。

【薬物動態】2.代謝

フルバスタチンはヒト肝ミクロソームにより水酸化体及び脱イソプロピル化体へと代謝され、水酸化及び脱イソプロピル化には主としてCYP2C9が関与している。

Table 8-1

プラバスタチンの添付文書：2004年7月改訂（第9版）：販売開始1989年10月

【使用上の注意】3.相互作用

代謝に関する記載なし。

［併用注意］（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
免疫抑制剤 シクロスポリン等	急激な腎機能悪化を伴う横紋筋融解症があらわれやすい ［自覚症状（筋肉痛、脱力感）の発現、CK(CPK)上昇、血中及び尿中ミオグロビン上昇を認めた場合は直ちに投与を中止すること。］	危険因子：重篤な腎障害のある患者

【薬物動態】 referenceあり

3.代謝

経口単回投与した時の尿（0.48時間）及び糞（0.96時間）中で、未変化体は尿中放射能の29%、糞中放射能の47.6%を占めていた。

4.薬物代謝酵素

本剤は、ヒト肝ミクロソームを用いたin vitro代謝試験において安定であり、チトクロームP450の分子種である3A4(CYP3A4)で代謝を受けなかったとの報告がある。

（1）CYP3A4の代謝を受ける薬剤に対する影響

本剤は、ヒト肝ミクロソームを用いたin vitro試験において、CYP3A4の基質であると報告されているニフェジピン、メキサゾラム、テストステロンの代謝に影響を与えなかったとの報告がある。

（2）CYP3A4を阻害する薬剤の影響

本剤の代謝は、CYP3A4を阻害する薬剤（イトラコナゾール、ジルチアゼム）との併用により、有意な影響を受けなかったとの報告がある。

（3）グレープフルーツジュースの影響

グレープフルーツジュースの反復飲用は、本剤の薬物動態に有意な影響を与えなかったとの報告がある。

Table 8-2

プラバスタチンの添付文書改訂案

【使用上の注意】3.相互作用

本剤は、ヒト肝ミクロソームを用いたin vitro代謝試験において安定であり、チトクロームP450の分子種である3A4(CYP3A4)で代謝を受けなかったとの報告がある。

［併用注意］（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
免疫抑制剤 シクロスポリン等	急激な腎機能悪化を伴う横紋筋融解症があらわれやすい ［自覚症状（筋肉痛、脱力感）の発現、CK(CPK)上昇、血中及び尿中ミオグロビン上昇を認めた場合は直ちに投与を中止すること。］	シクロスポリンが本剤の肝への取り込みを抑制し、血中濃度の増加すること(AUC: 5-12倍)が報告されている。危険因子：重篤な腎障害のある患者

【薬物動態】

3.代謝

経口単回投与した時の尿（0.48時間）及び糞（0.96時間）中で、未変化体は尿中放射能の29%、糞中放射能の47.6%を占めていた。

4.薬物代謝酵素

本剤は、ヒト肝ミクロソームを用いたin vitro代謝試験において安定であり、チトクロームP450の分子種である3A4(CYP3A4)で代謝を受けなかったとの報告がある。

（1）CYP3A4の代謝を受ける薬剤に対する影響

本剤は、ヒト肝ミクロソームを用いたin vitro試験において、CYP3A4の基質であると報告されているニフェジピン、メキサゾラム、テストステロンの代謝に影響を与えなかったとの報告がある。

（2）CYP3A4を阻害する薬剤の影響

本剤の代謝は、CYP3A4を阻害する薬剤（イトラコナゾール、ジルチアゼム）との併用により、有意な影響を受けなかったとの報告がある。

（3）グレープフルーツジュースの影響

グレープフルーツジュースの反復飲用は、本剤の薬物動態に有意な影響を与えなかったとの報告がある。

Table 9-1

ピタバスタチンの添付文書：2004年7月改訂（第3版）：販売開始2003年9月

【使用上の注意】3.相互作用

本剤は肝チトクロームP450(CYP)によりほとんど代謝されない（CYP2C9でわずかに代謝される）。

［併用禁忌］（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
シクロスポリン	急激な腎機能悪化を伴う横紋筋融解症等の重篤な有害事象が発現しやすい。	シクロスポリンにより本剤の血漿中濃度が上昇(Cmax 6.6倍、AUC 4.6倍)する。

［併用注意］（併用に注意すること）

記載なし。

【薬物動態】

1.健康成人における体内動態

（3）シクロスポリン併用投与時の血中濃度（引用文献あり）

健康成人男子6例に1日1回ピタバスタチンカルシウムとして2mgを6日間反復経口投与し、6日目のピタバスタチンカルシウム投与1時間前にシクロスポリン2mg/kgを単回経口投与したとき、血漿中濃度はAUCで4.6倍、Cmaxで6.6倍に増加した。

5.薬物代謝酵素（引用文献あり）

ピタバスタチンカルシウムは、ヒト肝ミクロゾームを用いた代謝試験においてわずかに代謝され、主にCYP2C9により8位水酸化体を生じた（in vitro）。

CYP分子種のモデル基質に対する阻害試験では、CYP2C9の基質のトルブタミド、CYP3A4の基質のテストステロンの代謝に影響しなかった（in vitro）。

Table 9-2

ピタバスタチンの添付文書改訂案

【使用上の注意】3.相互作用

本剤は肝チトクロームP450(CYP)によりほとんど代謝されない（CYP2C9でわずかに代謝される）。

［併用禁忌］（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
シクロスポリン	急激な腎機能悪化を伴う横紋筋融解症等の重篤な有害事象が発現しやすい。	シクロスポリンは本剤の肝への取り込みを抑制し、血漿中濃度が上昇(Cmax 6.6倍、AUC 4.6倍)する。

［併用注意］（併用に注意すること）

記載なし。

【薬物動態】

1.健康成人における体内動態

（3）シクロスポリン併用投与時の血中濃度（引用文献あり）

健康成人男子6例に1日1回ピタバスタチンカルシウムとして2mgを6日間反復経口投与し、6日目のピタバスタチンカルシウム投与1時間前にシクロスポリン2mg/kgを単回経口投与したとき、血漿中濃度はAUCで4.6倍、Cmaxで6.6倍に増加した。

5.薬物代謝酵素（引用文献あり）

ピタバスタチンカルシウムは、ヒト肝ミクロゾームを用いた代謝試験においてわずかに代謝され、主にCYP2C9により8位水酸化体を生じた（in vitro）。

CYP分子種のモデル基質に対する阻害試験では、CYP2C9の基質のトルブタミド、CYP3A4の基質のテストステロンの代謝に影響しなかった（in vitro）。

別添４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Saito M, Hirata-Koizumi M, Urano T, Miyake S, Hasegawa R	A literature search on pharmacokinetic drug interactions of statins and analysis of how this is reflected in package inserts of Japan.	J Clin Pharm Ther	30(1)	21-37	2005
Saito M, Hirata-Koizumi M, Matsumoto M, Urano T, Hasegawa R	Undesirable effects of citrus juice on pharmacokinetics of drugs – Focus on recent studies.	Drug Safety			2005 印刷中
Saito M, Hirata-Koizumi M, Miyake S, Hasegawa R	Comparison of information on pharmacokinetic interaction of Ca antagonists between quantitative data in the published literature and package inserts of Japan, USA and UK.	Eur J Clin Pharmacol			投稿中

Journal of Clinical Pharmacy and Therapeutics (2005) 30, 21–37

A literature search on pharmacokinetic drug interactions of statins and analysis of how such interactions are reflected in package inserts in Japan

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SUMMARY

Background and objectives: Statins (HMG-CoA reductase inhibitors) are one of the most widely prescribed classes of drugs throughout the world, because of their excellent cholesterol-lowering effect and overall safety profile except for rare but fatal rhabdomyolysis arising either directly or indirectly by pharmacokinetic interactions with certain other drugs. As package inserts in pharmaceuticals are the primary source of information for health care providers, we carried out a literature search to examine how crucial information was provided in package inserts of five statins approved in Japan (simvastatin, atorvastatin, fluvastatin, pravastatin and pitavastatin).

Methods: A MEDLINE search from 1996 to June 2004 was carried out to identify studies on clinical pharmacokinetic drug interactions for the five statins. We mainly collected information on area under plasma concentration (AUC) following co-administration of statins with other drugs. The current package inserts used in Japan were obtained from the website of the Pharmaceutical and Medical Device Agency whereas USA package inserts were obtained from the Food and Drug Administration website.

Results: The majority of package inserts listed the drugs that interacted with statins with most describing the risk of rhabdomyolysis because of the possibility of increases in blood concentration. However, quantitative information such as change in AUC was provided in only a few cases. Instructions for dosage adjustment are seldom provided in the Japanese package inserts. USA package inserts list almost identical drug interactions as the Japanese package inserts, although they contain more quantitative data, especially for typical cytochrome P450 (CYP) inhibitors.

Conclusion: All pharmacokinetic drug interactions including relevant quantitative data for potential effectors and details on mechanisms of interaction need to be given in package inserts as soon as the information becomes available, to ensure safe and proper use of the drugs concerned. Including such information in the package insert will be an extremely valuable aid for health care providers.

Keywords: drug information, drug interaction, literature search, package insert, safety use of drugs, statin

INTRODUCTION

Statins, or more specifically HMG-CoA reductase inhibitors, are used commonly for the treatment of lipid disorders as they are extremely effective in lowering cholesterol and have a good overall safety profile. Although long-term use of stains is well tolerated by the majority of patients, they may cause myopathy such as myalgia and myositis and rarely the serious condition, rhabdomyolysis. There is, however, no clear consensus of opinion on the complex mechanisms underlying statin-induced rhabdomyolysis (1). Although statins may cause rhabdomyolysis directly in a dose-dependent manner (2), the risk of statin-induced rhabdomyolysis and associated renal failure is considered to be higher with dynamic or kinetic interactions between statins and certain other drugs. For example, cerivastatin was withdrawn from the world market in

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2001 as it was shown in the United States to cause significant increases in death due to rhabdomyolysis (1) especially when administered concomitantly with gemfibrozil (3). Subsequent studies showed that this interaction increased blood concentration of cerivastatin. Other possible pharmacokinetic interactions with the statins that have been investigated include cyclosporin, macrolide antibacterials, human immunodeficiency virus protease inhibitors and azole antifungals (4–6). Given the role of pharmacokinetic drug interactions as a factor in statin-induced rhabdomyolysis it is extremely important that these drug interactions be closely managed (7, 8).

The drug package insert is the most basic tool for supplying information on drugs to health care providers. In order to avoid adverse effects induced by pharmacokinetic drug interactions, it is important to provide quantitative information on drug interactions in the package insert. The format and content of the package insert are governed by regulatory authorities in each region, based on scientific knowledge, medical preferences and history. Information on pharmacokinetic interactions is provided in the sections on precautions and drug metabolism. In 1993, concomitant use of sorivudine, a newly approved anti-viral drug, and fluorouracil, an anticancer drug, caused 23 cases of severe toxicity including 16 deaths in Japan as a result of fluoro-pyrimidine toxicity (9). These serial deaths which occurred soon after approval of the drug, became infamous in Japan, and led to many reforms of the Japanese drug regulatory systems (10, 11). Despite a warning statement that sorivudine should not be used in combination with anticancer drugs, this message was not highlighted clearly and did not specify the potential lethality of the interaction. After this tragedy, the drug interaction sections in the precautionary section of the package insert were revised to make them easier to understand. Current guidelines for package insert were established in 1997 (12–14) and stipulate that the drug interaction section should be prepared in tabular format, and also that the mechanism of interaction and their management must be indicated for each drug. Under these guidelines, 'Contraindication' means that the drugs must not be co-administered whereas 'Precaution' indicates that careful monitoring should be undertaken.

In this paper, we review published clinical pharmacokinetic drug interactions with statins and analyse whether or not the relevant information is reflected in the package inserts distributed in Japan. We also compared the Japanese package inserts with package inserts used in the USA, as several statins were developed by USA-based companies and the USA is the biggest market for statins. The content of USA package inserts is governed by 21 C.F.R. Sect. 201·56 to 57 with the information provided in the warning and drug interactions sections.

METHOD

A MEDLINE search from 1966 to June 2004 was carried out to identify studies on clinical pharmacokinetic drug interaction studies for the five statins approved in Japan, simvastatin, atorvastatin, fluvastatin, pravastatin and pitavastatin. We collected information on area under the blood concentration–time curve (AUC) and maximum blood concentration (C_{max}) for co-administration of statins and grapefruit juice or the following 28 drugs; itraconazole, fluconazole, ketoconazole, erythromycin, clarithromycin, azithromycin, ritonavir, saquinavir, nelfinavir, cyclosporine, fenofibrate, gemfibrozil, rifampicin, verapamil, diltiazem, mibefradil, cimetidine, ranitidine, omeprazole, propranolol, diclofenac, troglitazone, pioglitazone, irbesartan, tolbutamide, glibenclamide, warfarin and digoxin. Although the protocols were different in each study, the ratio of AUC with and without co-administration was used primarily as the best parameter for comparing published information with those in the package inserts.

The current package inserts used in Japan were obtained from the website of the Pharmaceuticals and Medical Device Agency (http://www.pmda.go.jp) whereas the USA package inserts were obtained from the Food and Drug Administration website (http://www.fda.gov). Each web site was accessed in May 2004. An additional data search was conducted using MEDLINE and Japana Centra Revuo Medicina (Japan Medical Abstracts Society) when information in the package inserts was not found in the first search.

RESULTS

Five statins, simvastatin, atorvastatin, fluvastatin, pravastatin and pitavastatin are currently on the

market in Japan. The chemical structure of these drugs is shown in Fig. 1, whereas the year of approval and dosage of each statin registered in Japan and the USA, and the enzymes involved in metabolism of the drugs are summarized in Tables 1 and 2, respectively. Information from the literature on pharmacokinetic drug interactions and statements contained in the packages of each of the statins are summarized in Tables 3–7. Each table contains all the drugs with pharmacokinetic interactions found either in the literature search or on the Japanese package inserts. For convenience, we classify the strength of interaction into the following three classes on the basis of changes in AUC. This classification system is similar to that used for CYP3A4 inhibitors in the midazolam

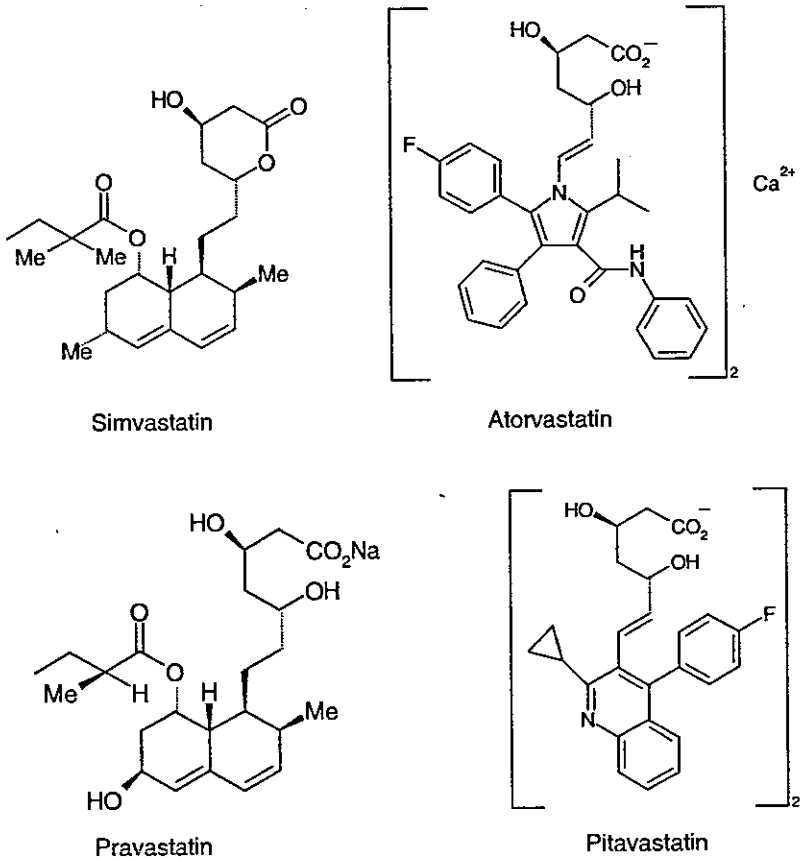

Fig. 1. Chemical structures of statins.

Table 1. Dosage and year of approval of statins

	Japan		USA	
	Dose (mg/day)	Approval year	Dose (mg/day)	Approval year
Simvastatin	5–20[a]	1991	5–80	1991
Atorvastatin	10–40	2000	10–80	1996
Fluvastatin	20–60	1998	40–80[b]	1993
Pravastatin	10–20	1991	40–80	1991
Pitavastatin	1–4	2003	Not approved	Not approved

[a]5–10 mg/day in original. Increased to 20 mg/day after amendment in 2001.
[b]Recommended starting dose is 20–40 mg/day.

Table 2. Enzymes involved in the metabolism of statins and their description in the package inserts

		Package insert (Japan)		Package insert (USA)	
	Responsible enzyme	Drug interaction	Pharmacokinetics	Drug interaction	Pharmacokinetics/ metabolism
Simvastatin	CYP3A4 (15)	CYP3A4	–	CYP3A4 (also in warning section)	CYP3A4
Atorvastatin	CYP3A4(15)	CYP3A4	CYP3A4	Cytochrome P450 3A4	Cytochrome P450 3A4
Fluvastatin	Mainly CYP2C9 (15, 16)	–	CYP2C9	2C9 (75%), 2C8 (5%), 3A4 (20%)	2C9 (75%), 2C8 (5%), 3A4 (20%)
Pravastatin	Not metabolized significantly by CYPs (15)	–	Not metabolized by CYP 3A4	Not metabolized by cytochrome P450 3A4	–
Pitavastatin	Metabolized slightly by CYP2C9(17, 18)	Hardly metabolized (slightly metabolized by CYP2C9)	Slightly metabolized (CYP2C9)	Not approved	Not approved

study (19) with one to twofold as weak, two to fivefold as moderate, and greater than fivefold as strong.

Simvastatin

In the literature column, the extent of changes in AUC for simvastatin resulting from interactions with a number of other drugs is given. Itraconazole, erythromycin, human immunodeficiency virus (HIV) protease inhibitors (ritonavir plus saquinavir soft-gel capsules), nelfinavir, cyclosporin, and diltiazem showed strong interactions, whereas gemfibrozil and verapamil showed moderate, troglitazone weak, and pioglitazone and irbesartan no interactions. In contrast, rifampicin induced a large drop in simvastatin's AUC. With regard to digoxin, simvastatin caused a small increase in the AUC for digoxin without any change in its own AUC. Unexpectedly, grapefruit juice had a moderate effect when taken in regular volume but a strong effect when high volumes were consumed (Table 3).

The Japanese package insert listed the metabolic enzyme CYP3A4 in the drug interaction section (Table 2). Itraconazole and miconazole were classified as contraindicated drugs for co-administration with simvastatin because they both increased the risk of rhabdomyolysis by inhibiting CYP3A4 metabolism. No quantitative information was provided for either drug, although as miconazole is the same type of CYP3A4 inhibitor as itraconazole, this information may have been relevant. Precautions regarding co-administration were listed for erythromycin, clarithromycin, cyclosporin and HIV protease inhibitors such as ritonavir, because of the risk of rhabdomyolysis from potential inhibition on CYP3A4 metabolism. However, no quantitative information was provided, and there was also no explanation on the rationale used to classify the drugs with strong potency as either contraindicated or precautionary. Cyclosporin was the only drug with a precautionary statement that dose adjustment should 'not exceed 10 mg/day', although no specific reason was given to support this statement. None of the other drugs with pharmacokinetic interactions documented in the literature were listed in the package inserts. Although there was a statement on pharmacokinetic interaction with grapefruit juice, no information on changes in the AUC for simvastatin were provided despite the intake volume of grapefruit juice being defined. Furthermore, this information may be easily ignored as it was located in a separate section labelled 'Other precautions', following the 'Other adverse effects' section. This section was separate from the information on drug interactions section but formed part of the precaution chapter.

The package insert from the USA listed the names of all the strong and moderate effectors cited

Table 3. Pharmacokinetic information on simvastatin drug interactions and the description in the package insert

		Japan			USA		
	Literature: changes in AUC	Status	Mechanism	Quantitative data/ dose adjustment	Section of statement	Mechanism	Quantitative data/ dose adjustment
Itraconazole	10–19-fold (15, 20)	Contraindication	Inhibition of CYP 3A4	–	Warning	Potent inhibitor of CYP 3A4	–
Miconazole	No report	Contraindication	Inhibition of CYP 3A4	–	Warning	Potent inhibitor of CYP 3A4	–
Erythromycin	6·2-fold (21)	Precaution	Possible CYP3A4 inhibition	–	Warning	Potent inhibitor of CYP 3A4	–
Clarithromycin	No report	Precaution	Possible CYP3A4 inhibition	–	Warning	Potent inhibitor of CYP 3A4	–
Ritonavir + Saquinavir[a]	31-fold (22, 23)	Precaution (As HIV Protease inhibitors)	Possible CYP3A4 inhibition	–	Warning	Potent inhibitor of CYP 3A4	–
Nelfinavir	6-fold (24)						
Cyclosporine	3–8-fold (25–27)	Precaution	Possible CYP3A4 inhibition	Not to exceed 10 mg/day	Warning	Potent inhibitor of CYP 3A4	Should not exceed 10 mg/day
Gemfibrozil[b]	2-fold (28)	–			Warning	–	Should not exceed 10 mg/day
Rifampicin	0·10-fold (29)	–			–		
Verapamil	4·6-fold (21)	–			Warning	–	Should not exceed 20 mg/day
Diltiazem	5-fold (30)	–			–		
Troglitazone[c]	0·6-fold (31)	–			–		
Pioglitazone	No change (31)	–			–		
Irbesartan	No change (acid form)(32)	–			–		
Digoxin	1·20-fold (AUC of digoxin) (33)	–			Drug interactions	–	Slight elevation of digoxin in plasma (<0·3 ng/mL)
Grapefruit juice	3·6–16-fold (34–36)	Other precautions	–	A report of clinical study[d]	Warning	Potent inhibitor of CYP 3A4	<1 quart (0·95 L) of grape fruit juice, Study 1: 16-fold Study 2: 1·88-fold

–, No data.
[a]Ritonavir plus saquinavir soft-gel capsules.
[b]Not approved in Japan.
[c]Withdrawn from Japan and US in 2000.
[d]It has been reported that a large amount (>1·14 L daily) of grapefruit juice increases blood simvastatin level.

Table 4. Pharmacokinetic information on atorvastatin drug interactions and the description in the package insert

		Japan			USA		
	Literature: changes in AUC	Status	Mechanism	Quantitative data/ dose adjustment	Section of statement	Mechanism	Quantitative data/ dose adjustment
Itraconazole	2·5–4-fold (37, 38)	Precaution	Inhibition of metabolism	–	Warning	–[d]	–
Erythromycin	1·33-fold (C_{max}: 1·38-folds) (39)	Precaution	Inhibition of metabolism	–	Warning	inhibition of CYP3A4	40% increase (as plasma concentration)
Azithromycin	No change (5)	–			–		
Clarithromycin	1·8-fold (5)	Precaution	Inhibition of metabolism	Increase 81·8%	–		
Ritonavir + Saquinavir[a]	3·5-fold (22)	Precaution (As HIV Protease inhibitors)	Inhibition of CYP 3A4	1·7-fold (Nelfinavir)	–		
Nelfinavir	1·7-fold (24)				–		
Cyclosporine	6-fold (activity)[c] (40)	Precaution	Inhibition of metabolism and bile exclusion	–	Warning	–[d]	–
Cimetidine	No change (41)	–			Drug interactions	–	not altered (plasma concentration)[c]
Troglitazone[b]	0·67-fold (42)	–			–		
Digoxin	1·15-fold for digoxin (43)	Precaution	Inhibition of digoxin exclusion via P-glycoprotein	3·6–14·8% (digoxin AUC)	Drug interactions	–	20% increase (steady-state plasma digoxin concentration)
Grapefruit juice	1·4–2·5-fold (44, 45)	–			–		

–, No data.
[a]Ritonavir plus saquinavir soft-gel capsules.
[b]Withdrawn from the market in Japan and USA.
[c]HMG-CoA reductase inhibitory activity (parent drug and metabolites).
[d]Risk of rhabdomyolysis.

Table 5. Pharmacokinetic information on fluvastatin drug interactions and the description in the package insert

		Japan			USA		
	Literature: changes in AUC	Status	Mechanism	Quantitative data/ dose adjustment	Section of statement	Mechanism	Quantitative data/ dose adjustment
Itraconazole	No change (46)	–			Drug interactions	CYP 3A4 inhibitor/ substrate	Does not affect plasma levels
Fluconazole	1·84-fold (47)	–			–		
Ketoconazole[a]	No change (16)	–			–		
Erythromycin	No change (16)	Precaution	–		Warning	CYP 3A4 inhibitor/ substrate	Did not affect steady-state plasma levels
Cyclosporine	3–3·3-fold (48, 49)	Precaution	–		Warning	CYP 3A4 inhibitor/ substrate	AUC: 1·9-fold, C_{max}: 1·3-fold
Bezafibrate	No report	Precaution	Possible high plasma level via inhibition of liver metabolism	–	Warning	–[c]	–
Gemfibrozil[b]	No change (50)	–			Warning	–	No change in plasma levels
Rifampicin	0·5-fold (16)	Precaution	Induction of liver metabolic enzyme	–	Drug interactions	–	0·49-fold
Cimetidine	1·24–1·33-fold (16)	Precaution	Possible high plasma level via inhibition of liver metabolism	–	Drug interactions	–	1·24–1·33-fold
Ranitidine	1·24–1·33-fold (16)	Precaution	Possible high plasma level via inhibition of liver metabolism	–	Drug interactions	–	1·24–1·33-fold
Omeprazole	1·24–1·33-fold (16)	Precaution	Possible high plasma level via inhibition of liver metabolism	–	Drug interactions	–	1·24–1·33-fold
Propranolol	No change (51)	–			Drug interactions	–	No change in bioavailability
Diclofenac	1·1–1·54-fold for fluvastatin, 1·1–1·3-fold for diclofenac (16, 52)	–			Drug interactions	–	1·3-fold for diclofenac AUC
Tolbutamide	No change (53)	–			Drug interactions	–	Did not affect

Table 5. Continued

	Literature: changes in AUC	Japan			USA		
		Status	Mechanism	Quantitative data/ dose adjustment	Section of statement	Mechanism	Quantitative data/ dose adjustment
Glibenclamide	No change (53)	–			Drug interactions	–	1·5-fold
Warfarin	No change for warfarin level (51)	Precaution	Not cleared	–	Drug interactions	–	No elevation of warfarin concentration
Digoxin	No change of digoxin AUC (54, 55), C_{max} of digoxin: 1·2-fold (56)	Precaution	Not cleared	–	Drug interactions	–	AUC: No change, C_{max}: 1·11-fold (for digoxin)

–, No data
[a]Only topical form is approved in Japan.
[b]Not approved in Japan.
[c]Fibrates alone associated with myopathy.

in the literature with the exception of diltiazem and rifampicin in the warning section on the increased risk of developing myopathy/rhabdomyolysis. Quantitative information was provided only for digoxin. For grapefruit juice, quantitative data of a 16-fold increase (36) and a 1·88-fold increase (unpublished) were given in the warning section with a recommendation on the maximum volume of grapefruit juice that may be consumed concomitantly with simvastatin.

Atorvastatin

There is evidence that this statin has a strong interaction with cyclosporin, moderate interactions with itraconazole, ritonavir plus saquinavir soft gel capsules and grapefruit juice, whereas erythromycin, clarithromycin and nelfinavir have only weak potency. Troglitazone has been shown to induce a small reduction in the AUC of atorvastatin, whereas azithromycin and cimetidine have no effect. The AUC of digoxin has been reported to be increased marginally following co-administration of atorvastatin (Table 4).

The Japanese package inserts for atorvastatin stated the potential for inhibition of the metabolic enzyme CYP3A4 in the drug interaction section (Table 2), and without giving any quantitative data, cautioned against co-administration of itraconazole, erythromycin and cyclosporine because of the risk of rhabdomyolysis. A precaution was also stated for clarithromycin and HIV protease inhibitors on the basis of quantitative data on metabolic inhibition similar to that obtained from our literature search. Cimetidine and troglitazone were not listed, with the latter agent having been withdrawn from the market several years ago. Concurrent use with digoxin was listed as a precaution due to the possibility of an increase in plasma digoxin concentration resulting from inhibition of P-glycoprotein-mediated exclusion. Despite grapefruit juice having proven weak to moderate interactions with atorvastatin, no information was provided in the package insert.

In the USA package insert, although itraconazole, erythromycin and cyclosporine were listed in the warning section, only erythromycin was accompanied with quantitative data describing a 40% increase in the plasma concentration of atorvastatin. Despite clarithromycin, HIV protease inhibitors and grapefruit juice having similar or

Table 6. Pharmacokinetic information on pravastatin drug interactions and the description in the package insert

		Japan			USA		
	Literature: changes in AUC	Status	Mechanism	Quantitative data/ dose adjustment	Section of statement	Mechanism	Quantitative data/ dose adjustment
Itraconazole	Slight increase – 1·5-fold (20, 37)		No effect on pravastatin metabolism		Drug interactions	Inhibition of p-glycoprotein (also known as CYP 3A4 inhibitor)	AUC: 1·7-fold, C_{max}: 2·5-fold
Fluconazole	No change (47)	–			–		
Ritonavir + Saquinavir[a]	0·5-fold (23)	–			–		
Cyclosporine	5–12-fold (57, 58)	Precaution	–	–	Warning	–	Pravastatin level: increase (one study), cyclosporine level: no elevations, should begin 10 mg/day, maximum 20 mg/day
Fenofibrate	No change (59)	Precaution	(Synergistic adverse effect)	–	Warning	–[d]	–
Gemfibrozil[b]	2-fold (60)	–			Warning	–	Significant increase (metabolite)
Rifampicin	0·69-fold (61)	–			–		
Diltiazem	No effects (62)		No effect on pravastatin metabolism		Drug interactions	Weak CYP 3A4 inhibitor	No change
Mibefradil[c]	No change (63)	–			Drug interactions	CYP 3A4 inhibitor	–
Propranolol	0·77-fold (64)	–			–		
Digoxin	Increase for pravastatin, no change on digoxin (65)	–			Drug interactions	–	Digoxin bioavailability: not affected, AUC of pravastatin: tended to increase
Grapefruit juice	No change (44, 45)	–			–		

–, No data.
[a]Ritonavir plus saquinavir soft-gel capsules.
[b]Not approved in Japan.
[c]Not approved in Japan and withdrawn from the market in USA.
[d]Risk of rhabdomyolysis.

Table 7. Pharmacokinetic information on pitavastatin drug interactions and the description in the package insert

		Japan		
	Literature: changes in AUC	Status	Mechanism	Quantitative data/ dose adjustment
Cyclosporine	4·55-fold (66)	Contraindication	–	AUC: 4·6-fold, C_{max}: 6·6-fold
Fenofibrate	1·18-fold (67)	Contraindication (as fibrates)	Either drug are known to induce rhabdomyolysis	1·2-fold
Gemfibrozil[a]	1·44-fold (67)	–		1·4-fold
Grapefruit juice	1·16-fold (67)	–		

–, No data.
[a]Not approved in Japan.

even greater potency than erythromycin, these drugs were not listed. The drug interaction section contained a statement that cimetidine had no interaction with atorvastatin, whereas the quantitative data on digoxin interaction was the same as that provided in the Japanese package insert.

Fluvastatin

The literature search showed that cyclosporine was of moderate potency, fluconazole weak potency whereas diclofenac had no effect. No changes in the pharmacokinetics of fluvastatin were reported for itraconazole, ketoconazole, erythromycin, gemfibrozil, propranolol, tolbutamide and glibenclamide. Oral clearance of fluvastatin is increased by rifampicin, whereas the AUC for warfarin and digoxin is not affected by fluvastatin (Table 5).

The drug interaction section in the Japanese package insert did not include the major metabolic enzyme CYP2C9 although this information was contained in the section on drug metabolism (Table 2). No information on fluconazole, a specific inhibitor of CYP2C9, was provided. Cyclosporin and erythromycin are listed as precautions due to the risk of rhabdomyolysis although no quantitative data are provided. Bezafibrate is identified as a precaution as it has the potential to increase the concentration of fluvastatin in blood by inhibiting hepatic enzymes. This precaution is not backed up by quantitative information. Rifampicin is listed as a precaution because of the increased potential for oral clearance of fluvastatin. Although there are no reports of pharmacokinetic interactions in the literature, cimetidine, ranitidine and omeprazole are classified as precautions as they may also cause high statin blood concentrations by inhibition of hepatic enzymes. No quantitative data are provided with this precaution. Warfarin and digoxin are listed as precautions, with neither mechanism nor quantitative data provided. A list of drugs shown not to interact with fluvastatin is not provided.

The USA package insert lists erythromycin, cyclosporin and gemfibrozil in the warning section, accompanied by quantitative data for erythromycin (no change), gemfibrozil (no change) and cyclosporin (1·9-fold, decrease in value obtained from current literature data). As fibrates, bezafibrate is also listed in the warning section although no pharmacokinetic reason is given for this classification. Quantitative data for itraconazole, rifampicin, cimetidine, diclofenac, tolbutamide, glibenclamide, warfarin and digoxin are provided in the drug interaction section.

Pravastatin

The literature search demonstrated that only cyclosporin has strong interactions with pravastatin, with gemfibrozil having moderate, and itraconazole weak effects. The HIV protease inhibitors, ritonavir and saquinavir soft gel capsules, rifampicin and propranolol decreased the AUC for pravastatin. Although the AUC for pravastatin was increased by digoxin, the AUC of digoxin was not affected by pravastatin. Fluconazole, fenofibrate, diltiazem, mibefradil and grapefruit juice were reported to have no effect on the AUC of pravastatin (Table 6).

The drug interaction section in the Japanese package insert does not provide any information

on metabolism of pravastatin (Table 2). Cyclosporin is listed as a precaution because of the risk of rhabdomyolysis although no pharmacokinetic reason is given for this classification. On the contrary, the pharmacokinetic section states that pravastatin is not metabolized by CYPs and that itraconazole and diltiazem therefore have no effect on pravastatin metabolism.

Both cyclosporin and fenofibrate are listed in the warning section of the USA package insert, because of the risk of rhabdomyolysis. Gemfibrozil is also included in the warning section with information on the urinary extraction rate and pharmacokinetic changes affecting the active metabolite of pravastatin being provided in the drug interaction section. Dosage adjustment of pravastatin is recommended for concomitant use with cyclosporine but no quantitative data is provided. Itraconazole, digoxin, diltiazem, mibefradil or warfarin are listed in the drug interaction section with quantitative or detailed data, with the exception of mibefradil, which has been withdrawn from the market.

Pitavastatin

The only interaction studies reported for pitavastatin are cyclosporine, fenofibrate, gemfibrozil and grapefruit juice. All the original reports are written in Japanese, and none is cited in MEDLINE. Cyclosporin has moderate interactions with pitavastatin, gemfibrozil has weak effects, whereas fenofibrate and grapefruit juice have no effect (Table 7).

The Japanese package insert states that pitavastatin is metabolized to a minor degree by the metabolic enzyme CYP2C9 (Table 2). Cyclosporin is listed as a contraindication because of the risk of rhabdomyolysis with no quantitative data being provided. Fibrates are also stated as a contraindication because both pitavastatin and fibrates may induce rhabdomyolysis, rather than for any pharmacokinetic interaction between the two drugs. Quantitative data for fenofibrate and gemfibrozil are contained in the pharmacokinetics section. Pitavastatin is not approved in the USA.

DISCUSSION

Drug interactions are one of the most important consideration in the safe and proper use of medicines. Interactions involve toxicodynamics, such as synergistic or additive adverse effects, and pharmacokinetics, such as an increase or decrease in the concentration of the drug in the blood. These latter changes are evaluated by quantitative data from clinical pharmacokinetic interaction studies. It is possible that such studies do not always predict actual drug interactions in patients as they usually adopt a cross-over design, are conducted in a small number of young healthy volunteers and use single-dose administration of the target drug. Furthermore, the studies are subject to publication bias with positive data more likely to be published than negative data (68). However, the results of all studies should be taken into account as this data may at the very least indicate a potential drug interaction under certain conditions. We believe that such information, if clearly presented in drug package inserts, would be very helpful to health care providers.

Some Japanese package inserts for statins give no information on drug metabolic enzymes in the drug interaction section. This lack of information may make it very difficult for health care providers to have a clear understanding of this potential interaction. Of the pharmacokinetic interactions, inhibition or induction of CYP enzymes, particularly CYP3A4, is probably the most common cause of documented drug interactions (69, 70), with several drugs having been withdrawn from the market as a consequence of serious adverse effects resulting from CYP-mediated interactions (71). This type of interaction is therefore a major consideration in the safe and proper use of statins and accordingly the majority of health care providers would refer only to the precautionary chapter including the drug interaction section when prescribing or dispensing these drugs. We consider that the lack of information on the metabolic enzymes in this section is unhelpful.

The strength of any warnings relating to co-administration status of drugs do not always reflect the strength of interaction between the drugs, with moderate or even strong pharmacokinetic interactions not being detailed in the package inserts in some cases. For example, a large amount of grapefruit juice (35, 36) and HIV protease inhibitors (ritonavir plus saquinavir soft-gel capsules) (23) increases plasma simvastatin levels more than 10-fold. This is comparable with the

increase seen with itraconazole. However, the warnings in the package insert are very different, with itraconazole being contraindicated, whereas grapefruit juice and HIV protease inhibitors are listed as precautions. Some discrepancy in the strength of any warnings and reported pharmacokinetic effects may be explicable. For example, although there is no pharmacokinetic interaction data reported for simvastatin and clarithromycin there is a report of rhabdomyolysis associated with combination therapy with the two drugs (72).

Instructions for dosage adjustment in the Japanese package inserts are provided only for one combination of drugs, simvastatin and cyclosporin. In contrast, the USA package inserts provide instructions for five combinations (including one combination with gemfibrozil which is not approved in Japan), sometimes accompanied by quantitative data. Furthermore, the USA package inserts provide more quantitative information for typical CYP inhibitors, even though these interactions are of weak potency. For example, data from two discrepant studies are provided for simvastatin and grapefruit interaction in the USA, whereas the Japanese package inserts just lists the results from the study incorporating higher doses without quantitative data. In addition, the mechanism of action for most drug combinations is not specified in the Japanese package inserts and is expressed merely as 'may increase plasma concentration' or ' risk of rhabdomyolysis'.

Although the published data on interactions, reviewed above, is helpful to health care providers for assessing the significance of any interactions, and for selecting safer alternatives, further studies are required for clarifying the mechanisms of drug interactions. This is especially relevant to interactions with fibrates as these agents may induce rhabdomyolysis by themselves (73) and the data is controversial. Despite numerous reports of rhabdomyolysis associated with combined statin and fibrate therapy (4, 74), any increase in statin's AUC with gemfibrozil is not as high as that seen with macrolides or azole antifungals (50, 60, 75, 76). There is evidence from *in vivo* studies that gemfibrozil alters the pharmacokinetics of other drugs by inhibiting CYP2C9 (77, 78), whereas an *in vitro* study showed that it was unlikely to inhibit other CYP isoforms (79). It has also been shown in human liver microsome that gemfibrozil inhibits glucuronidation of statins and its metabolites by UDP-glucuronyltransferase (UGT) (80). Other fibrates, such as fenofibrate, clofibrate and ciprofibrate are also metabolized by UGT (78), and it is possible that inhibition of this elimination pathway may be a cause of statin-fibrate interactions. Further *in vivo* studies are required to verify this mechanism. A recent *in vitro* study on rosuvastatin, a compound metabolized to a minor degree by CYP2C9 (81), indicated that gemfibrozil may interact with statins via organic anion transporter polypeptides (OATPs). This hypothesis is attractive, as various statins metabolized by different CYPs or indeed unaffected by CYPs, are affected to similar extents by gemfibrozil (82). Despite interactions between certain combinations of statins and fibrates leading to relatively large increases in AUC, this mechanism does not fully explain the marked increase in the prevalence of rhabdomyolysis.

Recently, it has been reported that P-glycoprotein and OATPs also influence the pharmacokinetics of statins, thereby making it difficult to predict quantitative drug interactions from CYP data alone. P-glycoprotein functions as a biological barrier by enhancing the excretion of xenobiotics including drugs from the liver or renal tubules into the adjacent luminal spaces (83). Both CYP3A4 and P-glycoprotein have similar substrates and inhibitor profiles, and many drug interactions involve both of these proteins. For example, cyclosporin is a substrate for both CYP3A4 and P-glycoprotein (84, 85) whereas statins are also substrates (86–89) and inhibitors of P-glycoprotein (90). Other transporters involved in drug pharmacokinetics are OATPs that function as multispecific carriers capable of bi-directional transport across the sinusoidal liver membrane (91). Uptake of statins across this membrane has been shown to be mediated by certain members of the OATP family (92, 93). A recent *in vitro* study suggests that another OATP family protein called OATP-B, located at the apical membrane of small intestinal epithelial cells, mediates pravastatin absorption in a pH-dependent manner (94, 95). These findings indicate that P-glycoprotein and OATPs are crucial for intestinal absorption, hepatic uptake and biliary secretion of statins and concomitant drugs. This mechanism may explain the interaction between cyclosporin and pravastatin or pitavastatin, despite the fact that

neither drugs is metabolized by CYP3A4. There is clearly a need for further information on the role of these transporters in the pharmacokinetics of statins.

The differences in information content of package inserts for each statin between regions may reflect differences in regulatory requirements and timing of drug development. Current guidelines for drug interaction studies were established in 2001 in Japan (96), and in 1997 [*in vitro* (97)] and 1999 [*in vivo* (98)] in the USA. It is possible that license holders may therefore not have conducted pharmacokinetic interaction studies during the drug developmental stage. In addition, most of the interaction studies were published in the late 1990s or thereafter. In our study we did not distinguish whether information contained in the current package inserts was first-time presentations or amended versions. However, license holders have an obligation to provide current scientific knowledge without regard to the date of approval of the drug.

Another difference between the Japanese and USA package inserts was that higher dosages of statins are listed occasionally in the USA package inserts (Table 1). Although this would be expected to result in a lower incidence of drug interactions in Japan, this was not seen possibly because of the lower body weight of Japanese people and the fact that cases of rhabdomyolysis are rare.

One of the characteristics of the Japanese package insert is the use of tables in the drug interaction section to improve clarity. The Japanese guidelines also require the package insert to be 'as simple as possible', leading to Japanese license holders omitting data in order to comply with this requirement. This is generally acceptable, but may have gone too far regarding information on drug interactions with important quantitative information on pharmacokinetic drug interactions missing. We consider that such crucial information should be incorporated in the Japanese package inserts.

CONCLUSION

Many studies have demonstrated pharmacokinetic interactions between statins and CYP inhibitors. In addition, some transporters, P-glycoprotein and OATPs may also contribute to observed pharmacokinetic changes. Japanese package inserts contain an incomplete list of drugs that interact with statins, usually only citing the risk of rhabdomyolysis resulting from an increase in the concentration of the drug in the blood. With a few exceptions, no quantitative information is provided or the potency of the interaction is not documented adequately. In comparison, USA package inserts which list almost identical drug interactions include more quantitative data. We recommend that Japanese package inserts need to reflect current information better including details of the mechanisms of action.

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