Table I. Relationships between investigational drugs and article index which reports clinical drug interaction studies involving CYP3A4 used as the data source

inhibitor	substrate													
	alprazolam	atrovastatin	buspirone	cerivastain	cyclosporin	felodipine	lovastatin	midazolam	nifedipine	nisoldipine	simvastatin	telithromycin	triazolam	zolpidem
azithromycin	-	4	-	-	-	-	-	11, 77, 78	-	-	-	-	31	-
cimetidine	1, 62	-	-	55	-	-	-	19, 21	42, 43	69	-	-	1, 18, 25, 62	36
clarithromicin	-	4, 37	-	-	-	-	-	27, 77		-	37	-	31	-
diltiazem	-	-	49	-	5, 23	-	7	8	67	-	54	-	47, 72	-
erythromycin	75	66	45	55	24, 34	12	-	58, 78	-	-	39	-	31, 61	52
fluconazole	-	-	-	-	16	-	-	57	-	-	-	-	70	32
fluoxetine	29, 51	-	-	-	-	-	-	48	-	-	-	-	74	3
fluvoxamine	22	-	50	-	-	-	-	48	-	-	-	-	-	-
gatifloxacin	-	-	-	-	-	-	-	28	-	-	-	-	-	-
itraconazole	76	40, 53	45, 46	41, 53	-	38	44, 56	2, 10, 57, 59	-	-	56	6, 65	71	32
ketoconazole	30	-	-	-	15, 23, 26	-	-	17, 48, 59, 68	-	35	-	6	30, 71, 73	32
nefazodone	33	-	-	-	-	-	-	48	-	-	-	-	13	-
ranitidine	-	-	-	-	-	-	-	19, 20, 21	42, 43	-	-	-	-	36
roxithromycine	-	-	-	-	-	-	14	9	-	-	-	-	-	-
saquinavir	-	-	-	-	-	-	-	60	-	-	-	-	-	-
telithromycin	-	-	-	-	-	-	-	6	-	-	6	-	-	-
verapamil	-	-	49	-	-	-	-	8	-	-	37, 39	-	-	-
voriconazole	-	-	-	-	63	-	-	64	-	-	-	-	-	-

Refer to Table II for each article.

The underlined indexes indicate that the results of the corresponding report were used to calculate the ratio of contribution of CYP3A4 to oral clearance (CR_{3A4}) and time-averaged apparent inhibition ratio (IR_{3A4}).

The indexes without underline indicate that the results of the corresponding report were used to evaluate the propriety of the present method.

Table II. List of articles for clinical drug interaction studies involving CYP3A4 used as the data source

index	article
1	Abernethy et al., Psychopharmacology 1983;80:275-8
2	Ahonen et al., Br J Clin Pharmacol 1995;40:270-2
3	Allard et al., Drug Metab Dis 1998;26:617-22
4	Amsden et al., J Clin Pharmacol 2002;42:444-9
5	Asberg et al., Eur J Clin Pharmacol 1999;55:383-7
6	Aventis. Ketek (telithromycin) Tablets. 2005. (www.fda.gov/cder/foi/label/2005/21144s001,003lbl.pdf)
7	Azie et al., Clin Pharmacol Ther 1998;64:369-77
8	Backman et al., Br J Clin Pharmacol 1994;37:221-5
9	Backman et al., Eur J Clin Pharmacol 1994;46:551-5
10	Backman et al., Eur J Clin Pharmacol 1998;54:53-8
11	Backman et al., Int J Clin Pharmacol Ther 1995;33:356-9
12	Bailey et al., Clin Pharmacol Ther 1996;60:25-33
13	Barbhaiya et al., J Clin Psychopharmacol 1995;15:320-6
14	Bucher et al., Eur J Clin Pharmacol 2002;57:787-91
15	Butman et al., J Heart Lung Transplant 1991;10:351-8
16	Canafax et al., Transplantation 1991;51:1014-8
17	Chung et al., Clin Pharmacol Ther 2006;79:350-61
18	Cox et al., Biopharm Drug Dispos 1986;7:567-75
19	Elliott et al., Eur J Anaesthesiol 1984;1:245-51
20	Elwood et al., Br J Clin Pharmacol 1983;15:743-5
21	Fee et al., Clin Pharmacol Ther 1987;41:80-4
22	Fleishaker & Hulst, Eur J Clin Pharmacol 1994;46:35-9
23	Foradori et al., Transplant Proc 1998;30:1685-7
24	Freeman et al., Br J Clin Pharmacol 1987;23:776-8
25	Friedman et al., J Clin Pharmacol 1988,28:228-33
26	Gomez et al., Clin Pharmacol Ther 1995;58:15-9
27	Gorski et al., Clin Pharmacol Ther 1998;64:133-43
28	Grasela et al., Pharmacotherapy 2000;20:330-5
29	Greenblatt et al., Clin Pharmacol Ther 1992;52:479-86
30	Greenblatt et al., Clin Pharmacol Ther 1998;64:237-47
31	Greenblatt et al., Clin Pharmacol Ther 1998;64:278-85
32	Greenblatt et al., Clin Pharmacol Ther 1998;64:661-71
33	Greene et al., J Clin Psychopharmacol 1995;15:399-408
34	Gupta et al., Br J Clin Pharmacol 1989;27:475-81
35	Helnig et al., Eur J Clin Pharmacol 1999;55:57-60
36	Hulhoven et al., Int J Clin Pharm Res 1988;8:477-83
37	Jacobson, Am J Cardiol 2004;94:1140-6
38	Jalava et al., Clin Pharmacol Ther 1997;61:410-5
39	Kantola et al., Clin Pharmacol Ther 1998;64:177-82
40	Kantola et al., Clin Pharmacol Ther 1998;64:58-65

Table II. List of articles for clinical drug interaction studies involving CYP3A4 used as the data source (continued)

index	article
41	Kantola et al., Eur J Clin Pharmacol 1999;54:851-5
42	Khan et al., Br J Clin Pharmacol 1991;32:519-22
43	Kirch et al., Arch Toxicol Suppl 1984;7:256-9
44	Kivisto et al., Br J Clin Pharmacol 1998;46:49-53
45	Kivisto et al., Clin Pharmacol Ther 1997;62:348-54
46	Kivisto et al., Pharmacol Toxicol 1999;84:94-7
47	Kosuge et al., Br J Clin Pharmacol 1997;43:367-72
48	Lam et al., J Clin Pharmacol 2003;43:1274-82
49	Lamberg et al., Clin Pharmacol Ther 1998;63:640-5
50	Lamberg et al., Eur J Clin Pharmacol 1998;54:761-6
51	Lasher et al., Psychopharmacology (Berl) 1991;104:323-7
52	Luurila et al., Eur J Clin Pharmacol 1998;54:163-166
53	Mazzu et al., Clin Pharmacol Ther 2000;68:391-400
54	Mousa et al., Clin Pharmacol Ther 2000;67:267-74
55	Muck et al., Eur J Clin Pharmacol 1998;53:469-73
56	Neuvonen & Jalava, Clin Pharmacol Ther 1996;60:54-61
57	Olkkola et al., Anesth Analg 1996;82:511-6
58	Olkkola et al., Clin Pharmacol Ther 1993;53:298-305
59	Olkkola et al., Clin Pharmacol Ther 1994;55:481-5
60	Palkama et al., Clin Pharmacol Ther 1999;66:33-9
61	Phillips et al., J Clin Psychopharmacol 1986;6:297-9
62	Pourbaix et al., Int J Clin Pharmacol Ther Toxicol 1985;23:447-51
63	Romero et al., Clin Pharmacol Ther 2002;71:226-34
64	Saari et al., Clin Pharmacol Ther 2006;79:362-70
65	Shi et al., Pharmacotherapy 2005;25:42-51
66	Siedlik et al., J Clin Pharmacol 1999;39:501-4
67	Tateishi et al., J Clin Pharmacol 1989;29:994-7
68	Tsunoda et al., Clin Pharmacol Ther 1999;66:461-71
69	van Harten et al., Clin Pharmacol Ther 1988;43:332-41
70	Varhe et al., Br J Clin Pharmacol 1996;42:465-70
71	Varhe et al., Clin Pharmacol Ther 1994;56:601-7
72	Varhe et al., Clin Pharmacol Ther 1996;59:369-75
73	von Moltke et al., J Pharmacol Exp Ther 1996;276:370-9
74	Wright et al., Pharmacotherapy 1992;12:103-6
75	Yasui et al., Clin Pharmacol Ther 1996;59:514-9
76	Yasui et al., Psychopharmacology (Berl) 1998;139:269-73
77	Yeates et al., Int J Clin Pharmacol Ther 1996;34:400-5
78	Zimmermann et al., Arzneimittelforschung 1996;46:213-7

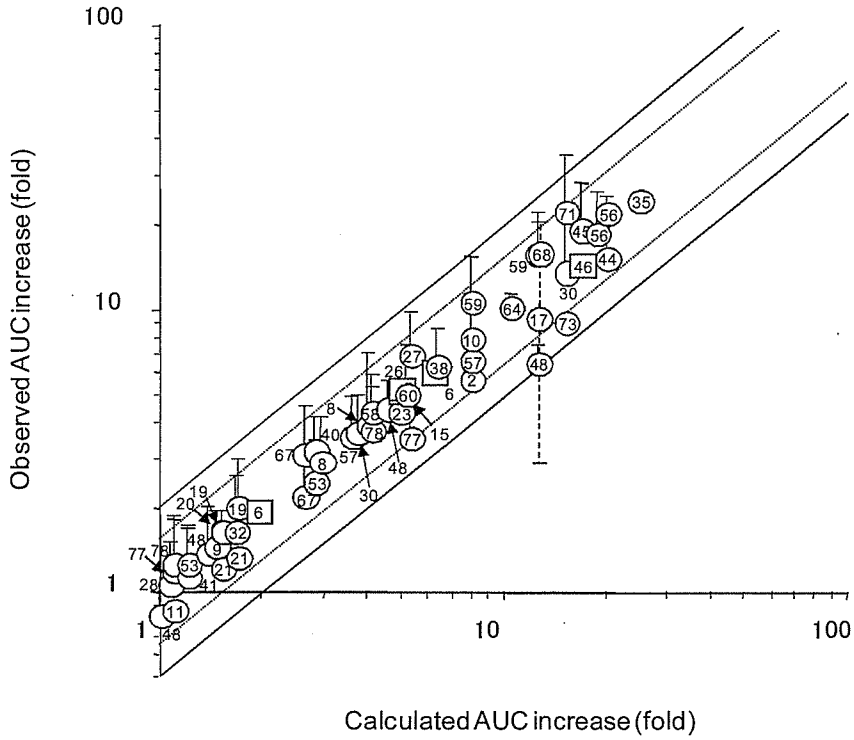
Table III. Calculated ratios of the contribution of CYP3A4 to the oral clearance (CR_{3A4}) of substrates

Substrate	CR_{3A4}
Simvastatin	1.00
Lovastatin	1.00
Buspirone	0.99
Nisoldipine	0.96
Triazolam	0.93
Midazolam	0.92
Felodipine	0.89
Cyclosporin	0.80
Nifedipine	0.78
Alprazolam	0.75
Atorvastatin	0.68
Telithromycin	0.49
Zolpidem	0.40
Cerivastatin	0.18

Table IV. Calculated ratios of the time-averaged apparent inhibition ratio of CYP3A4 (IR_{3A4}) for inhibitors

Inhibitor	daily dose	IR_{3A4}
Ketoconazole	200-400mg	1.00
Voriconazole	400mg	0.98
Itraconazole	100-200mg	0.95
Telithromycin	800mg	0.91
Clarithromycin	500-1000mg	0.88
Saquinavir	3600mg	0.88
Nefazodone	400mg	0.85
Erythromycin	1000-2000mg	0.82
Diltiazem	90-270mg	0.80
Fluconazole	200mg	0.79
Verapamil	240mg-480mg	0.71
Cimetidine	800-1200mg	0.44
Ranitidine	300-600mg	0.37
Roxithromycin	300mg	0.35
Fluvoxamine	100mg-200mg	0.30
Azithromycin	250-500mg	0.11
Gatifloxacin	400mg	0.08
Fluoxetine	20-60mg	0.00

A:


100
10
1
1
10
100
Observed AUC increase (fold)
Calculated AUC increase (fold)

B:

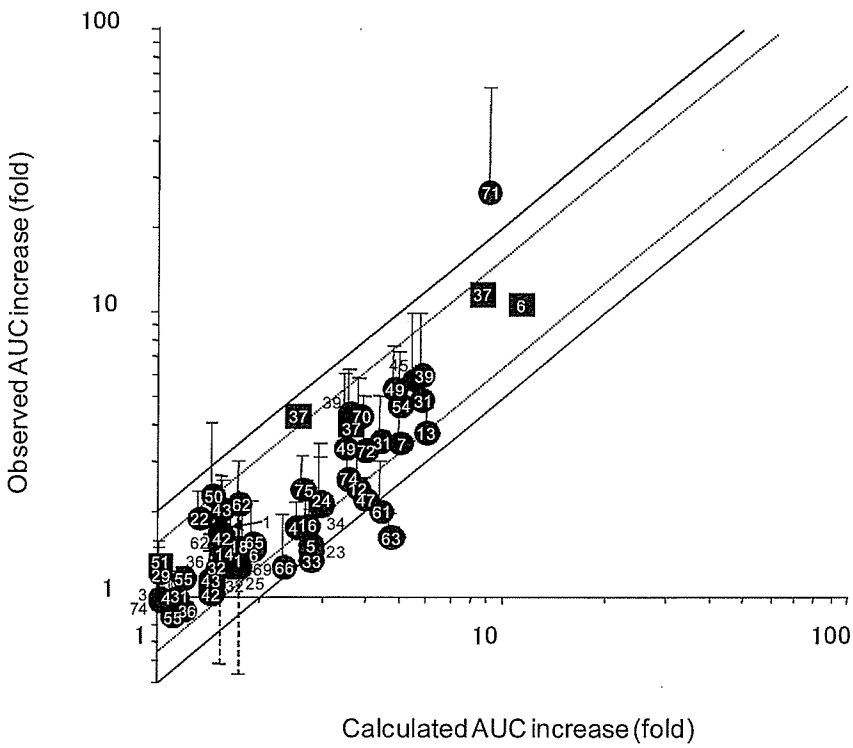

100
10
1
1
10
100
Observed AUC increase (fold)
Calculated AUC increase (fold)

Figure 1 ----- **Relationship between the observed and calculated increase in AUC by drug interactions.** Using the CR_{3A4} and IR_{3A4} values shown in Table III and IV, respectively, the increase in AUC of substrate drugs by drug interactions reported in 60 clinical studies, indicated by the indexes without underline in Table I, was predicted with Eq. 11 (Panel B). Panel A was prepared in the same style as Panel B, for the purpose of demonstrating the deviation of AUC values among 53 clinical studies, the mean values of which were used to determine the CR_{3A4} and IR_{3A4} values. The data source for Panel A is indicated by the underlined indexes in Table I. In Panels A and B, each circle and vertical bar represents the mean + S.D. values of subjects reported in each article. A dashed bar represents the range. If the S.D. values or the ranges were not reported in articles, the reported mean values were shown by squares. Solid and dotted lines represent 50-200% and 67-150% ranges, respectively, of the calculated increase.

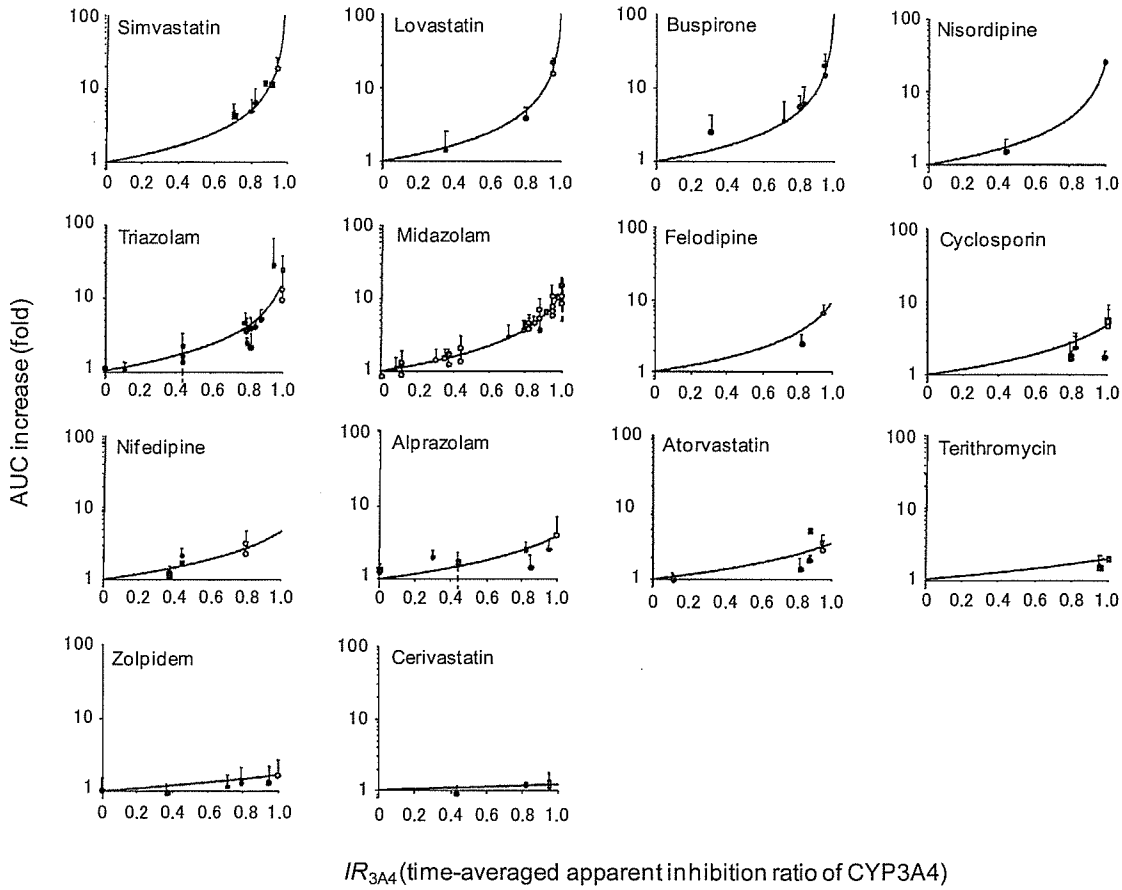


Figure 2 ----- Increase in the AUC reorganized for each substrate drug as a function of *IR* of inhibitors. Data shown in Fig. 1 were reorganized to show the increase in AUC of each substrate drug as a function of the IR_{3A4} values of inhibitors. Open and closed symbols represent the data set shown in Figs. 1A and 1B, respectively. See legends to Fig. 1 for details.

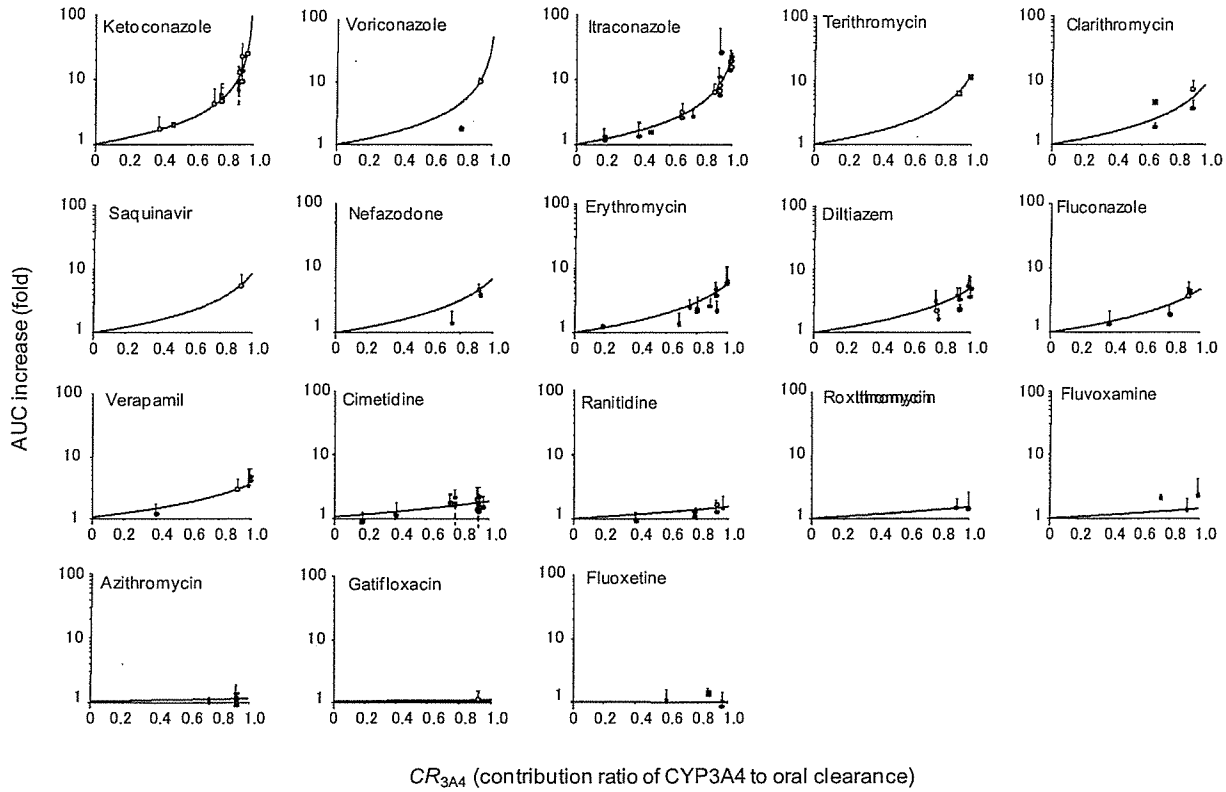


Figure 3 ----- Increase in the AUC of substrate drugs reorganized for each inhibitor as a function of the *CR* values of substrate drugs. Data shown in Fig. 1 were reorganized for each inhibitor to show the increase in AUC of each substrate drug as a function of the CR_{3A4} values of substrate drugs. Daily doses of inhibitors are indicated in parentheses. Open and closed symbols represent the data set shown in Figs. 1A and 1B, respectively. See legends to Fig. 1 for details.

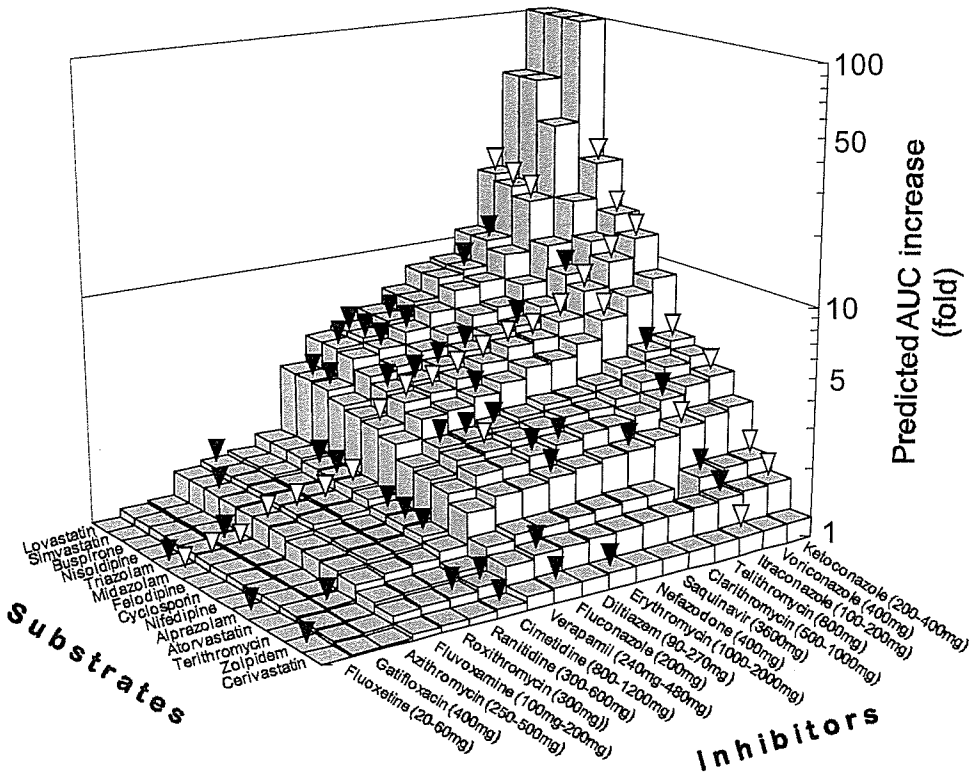


Figure 4 ----- Predicted increase in the AUC of substrate drugs by various drug interactions. The increase in AUC of substrate drugs by various drug interactions was predicted according to the CR_{3A4} and IR_{3A4} values shown in Table III amd IV, respectively. Open and closed arrows show the data set shown in Figs. 1A and 1B, respectively.

資料 4.

GENERAL PREDICTION OF DRUG-DRUG INTERACTIONS FROM INTERACTION WITH SELECTIVE INHIBITOR OR SUBSTRATE

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A framework is presented for prediction of oral drug-drug interactions which are mediated by hepatic drug metabolizing enzymes. Results of 112 *in vivo* drug-drug interaction studies which were mediated by primarily by CYP3A4 were collected from the literature, and we found that AUC increase (ΔAUC) by pharmacokinetic interaction between an inhibitor and a substrate is predictable from the apparent time-averaged inhibition ratio (IR) of the inhibitor and the contribution ratio for oral clearance (CR) of the substrate. IR was calculated from extents of an *in vivo* interaction observed between the inhibitor and selective substrates for CYP3A4 such as midazolam, and CR was calculated from extents of an interaction between the substrate and selective inhibitors for CYP3A4 such as itraconazole. A phamacokinetic consideration revealed that, once IR and CR values were obtained, predictions of ΔAUC for any combination of inhibitors and substrates are given by 1 / (1 – IR×CR). In the case of drug interactions mediated by CYP3A4, the most of predicted ΔAUC values were 50-200% of the actual increases

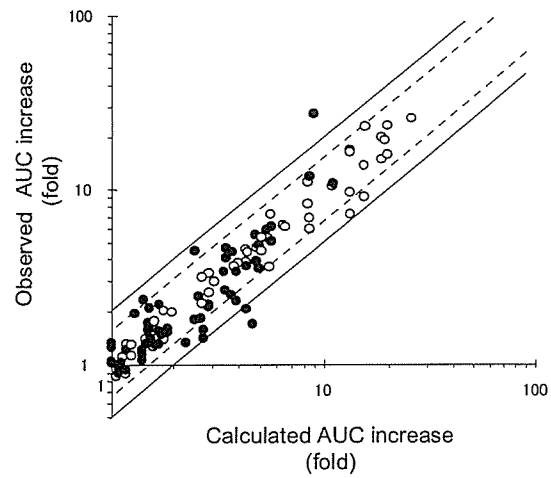

Fig. 1. Prediction of drug interactions mediated by CYP3A4. Open circles represent drug interactions which were used for construction of the model (midazolam with inhibitors). Close circles represent predicted drug interactions by the model. Dotted and straight lines indicate ±50% and ±100% deviations, respectively, from the calculated value.

(Fig. 1). In the analysis of CYP3A4, 14 substrates (midazolam, alprazolam, buspirone, cerivastatin, atorvastatin, cyclosporin, felodipine, lovastatin, nifedipine, nisoldipine, simvastatin, triazolam, zolpidem, and telithromycin) and 18 inhibitors (ketoconazole, voriconazole, itraconazole, telithromycin, clarithromycin, saquinavir, nefazodone, erythromycin, diltiazem, fluconazole, verapamil, cimetidine, ranitidine, roxithromycin, fluvoxamine, azithromycin, gatifloxacin, and fluoxetine) were used.

The same theory was applicable to other CYPs or hepatic drug metabolizing enzymes. In the case of CYP2D6, 14 substrates (flecainide, atenolol, metoprolol, propranolol, imipramine, desipramine, levofloxacin, carvedilol, propafenone, ritonavil, tolterodine, perphenazine, encainide and mexiletine) and 19 inhibitors (amiodarone, amitriptyline, chlorpromazine, cimetidine, citalopram, diltiazem, verapamil, diphenhydramine, fluoxetine, sertraline, fluvoxamine, hydoxychloroquine, labetalol, mexiletine, omeprazole, paroxetine, propafenone, quinidine, and retonavil) were selected for an analysis. CR values were primarily obtained from AUC increases which were observed in poor metabolizers of CYP2D6. IR values were calculated from interaction studies with typical substrates of CYP2D6 such as desipramine and metoprolol. For good predictions, an accurate evaluation of CR for each metabolizing enzyme is important. For CYP2C9 and CYP2C19 together with CYP2D6, pharmacokinetics in poor metabolizers would be useful information to estimate CR values. For these enzymes, selectivity of each substrate and inhibitor need to be considered carefully. In some cases, a drug interaction possibly occurs due to contributions of more than one metabolizing enzyme. By extending the current theory, an equation to predict AUC increases by multiple drug interactions was derived. The theory is also applicable to predict abrupt AUC increase by drug interactions in genetically poor or intermediate metabolizers. In general, CR values can be predicted in a relatively straightforward manner from *in vitro* experiments. Especially for new drugs, early estimation of CR would be very informative for rationale clinical development. On the other hand, prediction of IR values is more complicated.

This method would be applicable (1) to prioritize clinical trials to be carried out to investigate drug interactions in the course of drug development, (2) to help understanding descriptions of the labeling with regard to drug interactions, (3) and to

preliminarily estimate clinical significance of unknown drug interactions. We checked information described in the Japanese labeling, and found that some possible drug interactions have not been warranted even though apparent AUC increases are predicted by the current method. Further studies may be required to confirm clinical significance of such drug interactions.

資料 5.

CYP3A4 誘導薬の併用による CYP3A4 基質薬の臨床薬物動態変化の網羅的予測

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(日本薬学会第126年回要旨)

【背景・目的】CYP3A4 の誘導は、臨床的に無視できない薬効の減弱を惹起する場合があり注意が必要である。例えばリファンピシンは CYP3A4 を強く誘導し、そのために併用薬の血中濃度が 1/10 に減少することも少なくない。しかし、CYP3A4 の誘導による臨床薬物動態変化の報告は少なく、多くの薬で変化の程度を知るのが困難な状況にある。そこで本研究は、リファンピシン、セントジョーンズワートおよびカルバマゼピン等の CYP3A4 誘導薬・誘導剤の併用が、様々な CYP3A4 の基質薬の血中濃度をどの程度減少させるかを網羅的に予測する方法の開発を目的とした。

【方法】我々は CYP3A4 を介する薬物間相互作用による血中濃度の上昇を網羅的に予測する方法を既に報告しており<第 16 回日本医療薬学会年会講演要旨集,pp392,2006>、予測に基質薬の 3A4 のクリアランスへの寄与率 (CR_{3A4}) と阻害薬の阻害率 (IR_{3A4}) を用いた。この方法の拡張として、本研究では CYP3A4 酵素量の見かけの増加 (enzyme gain, EG_{3A4}) を誘導の指標とし、CR_{3A4} と組み合わせて予測に用いた。EG_{3A4} が 0 であれば誘導はなく、1 であれば酵素量は 2 倍に増えたと考える。誘導薬併用による基質薬を経口投与時の血中濃度曲線下面積 (AUC) の変化率は、基質薬の未変化体尿中排泄が無視できる場合には、$1/(1 + CR_{3A4} \times EG_{3A4})$で求められる。CYP3A4 の誘導薬による基質薬の血中濃度変化の報告を文献より収集し、最も高い CR_{3A4} を有する基質薬の AUC 変化率から誘導薬の EG_{3A4} を算出した。求めた EG_{3A4} から他の基質薬の AUC 変化率を予測し、観察値と比較してその予測精度を検証した。

【結果・考察】リファンピシン、セントジョーンズワートおよびカルバマゼピンに関して、算出された EG_{3A4} と CR_{3A4} を用いて、相互作用による基質薬物の AUC 変化率を予測したところ、観測値と良く一致した。本予測法は、CYP3A4 の誘導剤と基質薬物との相互作用の程度を網羅的に予測するのに有用であり、情報の乏しい組み合わせについて、その臨床的重要度を推定する手段になると考えられた。