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有害事象に関与する薬物動態相互作用に関する研究

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厚生労働科学研究費補助金（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）
有害事象に関与する薬物動態相互作用に関する研究

総合研究報告書

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研究要旨：薬物相互作用の情報提供に関する研究では、第二相代謝酵素やトランスポーターに関する情報は各国とも同程度で、今後の研究結果を添付文書に反映する必要がある。添付文書記載順序、相互作用の表形式は、高く支持されていた。相互作用が疑われる有害事象の報告総数は 86 症例あった。抗がん剤併用療法についての研究では、乳がんに用いるトラスツズマブ及び大腸がんに用いる 5-FU/l-LV、CPT-11、FOLFIRI、FOLFOX6 について有害事象を診療録から調査し、抗がん剤併用療法における有害事象発生の状況を明らかにし、予測可能性を検討した。薬物トランスポーター遺伝子発現系、ヒト腎組織切片を確立することで、in vitro 輸送実験により、取り込み過程の薬物間相互作用評価法を確立した。腎尿細管分泌の排出過程に働くトランスポーターが薬物間相互作用の対象となる例を in vitro および in vivo 実験により見いだした。さらに、医薬品による相互作用の発生において重要な要因となるヒト薬物代謝酵素と薬物トランスポーターの誘導現象を *in vitro* で評価できる培養細胞系を確立した。

A. 研究目的

有害事象に関わる薬物動態相互作用の添付文書による情報提供の現状と問題点を明らかとするため、第二相代謝酵素、トランスポーターを介した薬物相互作用について、各国添付文書、関連する文献情報の解析を行った。また、現在の添付文書の問題点の把握のために製薬企業及び医師に対し、記載方法、相互作用、薬物動態に関するアンケート調査を実施し，比較解析した。文献情報より 3 年分の相互作用が疑われる有害事象報告をとりまとめた。

抗がん剤併用療法については、HER II 蛋白陽性の乳がんの分子標的治療薬トラスツズマブに特徴的な有害事象の発生状況に関する調査を行い、抗がん剤治療歴や抗がん剤併用時等のリスクファクターを有する場合での心毒性、Infusion Reaction（IR）の

発生状況を明らかにするとともに、大腸がんの主要な治療レジメン毎に実施例を対象として有害事象データを集積し、発現状況を把握、添付文書と比較し、その情報を治療に反映させることによって、より安全な薬物治療に資することを目的とした。

複数の医薬品が併用される現在の薬物療法では、安全性確保のために薬物間相互作用が生じないことを確認することは必須である。本研究では、トランスポーターが関与する組織移行性・排出過程、消化管吸収過程における薬物間相互作用に注目し、そのメカニズムを解明することで、in vitroで定量的に評価するための試験系をたち確立することを目的とした。

さらに、医薬品による相互作用の発生において重要な要因となるヒト薬物代謝酵素と薬物トランスポーターの誘導を *in vitro* で評価できる実験系を確立するため、誘導に関与している複数の核内受容体を培養細胞に共発現させ、よりヒトに近い誘導能を持った *in vitro* 評価系の開発を試みた。

B. 研究方法

薬物相互作用の情報提供に関する研究では、第二相薬物代謝酵素及びトランスポーターを介した薬物動態相互作用について、日米英の添付文書の記載内容と、公表文献情報との比較・解析を行った。また、我が国の添付文書の様式及び記載事項に関し、日本製薬工業協会の協力を得て会員企業に対して郵送法によりアンケート調査を行った。医師については、(株)プラメドに委託してインターネットにより、同様のアンケート調査を行った。Pubmed により有害事象に係る相互作用の文献調査を行った。

抗がん剤併用療法に関する研究では、国立がんセンター中央病院におけるトラスツズマブ投与歴を有する乳がん患者（調査対象期間は 2001 年 6 月から 2006 年 12 月）及び大腸がん患者に対し用いた 4 レジメン（5-FU/l-LV、CPT-11、FOLFIRI、FOLFOX6 を対象（調査対象期間は 2003 年 4 月から 2005 年 12 月）とし、有害事象について診療録より情報収集を行って解析を行った。また、大腸がんについては 5-FU 注協和®、アイソボリン®注、トポテシン®注、エルプラット®注射用の製造販売業者の作成した添付文書及びインタビューフォーム(IF)から有害事象発生率を抽出した。

医薬品の体内動態における薬物間相互作用を予測するための研究では、ヒト腎組織切片や肝臓・腎臓への取り込み過程に働くトランスポーター（OATP1B3、OAT1、AOAT3)、排泄側トランスポーター(MRP2、MRP4、BCRP、MATE）の遺伝子発現系を用いた in vitro 輸送試験により医薬品の阻害定数の評価を行った。臨床投与量での非結合型薬物、排出過程の場合には安全マージンとしてその 10 倍の濃度に基づいて、薬物間相互作用が生じる可能性を評価した。核内受容体リガンド投与・非投与によるマウス in vivo 試験を行った。

また、ヒト *CYP3A4* 遺伝子や P-糖タンパク質遺伝子（*MDR1*）のプロモーター領域を用いたレポーター遺伝子と核内受容体の PXR および VDR の発現プラスミドをヒト肝臓由来細胞の HepG2 あるいは小腸由来の Caco-2 に導入し、レポーター遺伝子の転写活性を測定した。PXR および VDR

と遺伝子上の転写調節領域との結合は、ゲルシフトアッセイで測定した。

（倫理面への配慮）

抗がん剤併用療法の研究での個人情報の取り扱いは、「がんセンター保有個人情報管理規定」及び「国立がんセンターが扱う個人情報に関するガイドライン」に従った。その他の研究は添付文書および文献情報の解析、あるいは培養細胞を用いた実験であり、倫理面での問題はない。

C. 研究結果

日本の添付文書では10成分についてグルクロン酸抱合に関する注意または禁忌があり、日米英で同程度の情報提供がされていたが、機序等については、最新の研究成果に基づき記載すべきと思われた。各国のトランスポーターに関する記載分量は大きく変わらなかったが、記載内容は一致せず、また文献上の有害事象報告は添付文書に殆ど反映されておらず、研究結果の的確な反映が必要と考えられた。我が国の添付文書に関して、製薬企業、医師ともに、記載順序、相互作用の一覧表形式について高く支持されていた。一方、「代謝・輸送に関連する分子種の遺伝子多型」については、特に医師で必要とする回答が少なく、医療の場に十分に浸透していないことが伺われた。その他の回答内容は企業と医師で類似していたが、食品、医薬品との相互作用がある場合の添付文書改訂については、医師よりも企業の方が、情報の集積を待つ傾向があり、考え方に差が見られた。相互作用による有害事象報告は86症例あった。

抗がん剤併用療法に関する研究では、乳がんについて、対象患者321名のうち心障害発現症例は17名（5.3%）であった。メーカー使用成績調査(1142例のうち28例)と比較すると、RR = 2.16（1.20-3.89）となり本調査結果は、既存の情報よりも多く検出された。またIRは97例（30.2%）であり、メーカー使用成績調査（1142例のうち367例）との比較では発生割合に違いは見られなかった。心障害関連因子では、単変量解析にて関連性が推定された心疾患既往歴あり、遠隔転移あり、手術歴ありの3因子に関し多変量解析を行い、心疾患既往歴あり（オッズ比、95%CI、有意確率：6.027、1.270-5.100、P=0.006）が独立して心障害発現と関連していることが推定された。大腸がんについては、調査症例数はFOLFIRIが50例、それ以外のレジメンは100例でレジメン毎の平均治療コース数は5-FU/l-LVで17コース、CPT-11が7コース、FOLFIRIが9.5コース、FOLFOXが6コースと差がみられた。日常診療における有害事象発生率を添付文書・IFからは抽出した情報と比較したところ、臨床試験時設定が日常診療における標準投与量、投与間隔と一部が一致していた。しかし、副作用発現率は全体の副作用発生率で示されていた。

体内動態相互作用に関する研究では、ヒト腎組織切片を用いたin vitro輸送実験系を確立し、本評価系を用いてmethotrexateとNSAIDsやprobenecidによる阻害定数を測定した結果、一部の医薬品との薬物間相互作用は取り込み過程の阻害であることが示唆された。さらに、排出過程に働くMRP4も阻害することが示唆された。fexofenadineとcimetidineの相互作用では、cimetidineに

よるヒト腎組織切片への取り込み阻害は弱く、排出側の相互作用を仮定した。fexofenadine が MATE1 の基質となること、ならびに cimetidine が MATE1 阻害剤あることから、この薬物間相互作用が MATE1 の阻害であることが示唆された。15 種類の化合物で阻害実験を行った結果、臨床濃度を考慮すると、一部の医薬品は肝取り込み過程に働く OATP1B3 を阻害する可能性が示唆された。トランスポーターの発現誘導による薬物間相互作用として、PPARαリガンドの効果を検討した。PPARαアゴニスト（WY14643 と ibuprofen）を前投与したマウスでは、特に経口投与後の methotrexate の血漿中濃度 AUC が増加し、PPARαアゴニスト処理により消化管吸収過程の促進が生じていることが示唆された。methotrexate の消化管吸収に関わるトランスポーター PCFT、RFC、Mrp3、排出に働く Mrp2 の mRNA レベルは非投与群と同程度であった。

ヒト *CYP3A4* 遺伝子と P-糖タンパク質遺伝子（*MDR1*）のプロモーター領域を用いたレポーター遺伝子と核内受容体の PXR および VDR の発現プラスミドを培養細胞に導入し、レポーター遺伝子の転写活性を測定したところ、極めて鋭敏に種々の誘導剤による誘導能を評価することができた。また、*CYP3A4* や *MDR1* の転写活性化において、それぞれの遺伝子の転写調節領域の複数の部位に PXR と VDR は結合することや、PXR と VDR を同時に発現させた場合、PXR は VDR による転写活性を抑制するも明らかになった。

D. 考察・結論

第二相代謝酵素やトランスポーターの情報は、研究結果を適切に添付文書に反映する必要がある。添付文書の様式は、企業、医師に支持されていた。重篤副作用を起こす医薬品の組み合わせはデータベース化が必要である。

乳がんのトラスツズマブについて、心障害発現関連因子として、心疾患既往歴が推定された。また、大腸がんの抗がん剤併用療法について有害事象の添付文書との比較において投与法や支持療法の実施など条件の違いにより発生する有害事象と発生率に違いが生じる可能性が明らかとなった。

臨床で使用されている医薬品の中には、トランスポーターに対する阻害定数に比べて臨床血漿中濃度が十分高いものが含まれていた。これらの医薬品は in vivo でトランスポーター機能を阻害し、薬物間相互作用を生じうることが示唆された。トランスポーターに対する阻害定数、膜透過過程における寄与率には種差があることから、定量的な評価では実験動物ではなく、ヒト遺伝子発現系やヒト組織を利用することが必要である。

CYP3A4 あるいは P-gp の誘導能を持った *in vitro* アッセイ系を用いることによって、CYP3A4 や P-gp の誘導を介して生じる医薬品の相互作用を予測するためのアッセイ系として活用することが期待される

E. 健康危機情報

なし。

F. 研究発表

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G. 知的所有権の取得状況

なし。

別紙４

研究成果の刊行に関する一覧表

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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
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REVIEW ARTICLE

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Undesirable Effects of Citrus Juice on the Pharmacokinetics of Drugs

Focus on Recent Studies

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Abstract

It is well known that intake of grapefruit juice affects the pharmacokinetics of various kinds of drugs. It has been reported that other citrus juices also interact with certain drugs. To re-evaluate citrus juice-drug interactions based on currently available evidence, a literature search was conducted for new and updated information since the grapefruit juice-drug interaction was last reviewed in 1998. MEDLINE (1998–October 2004) was accessed and more than 200 reports were found. The effects of grapefruit juice ingestion on the pharmacokinetics of orally administered drugs have been reported for 40 drugs since the reviews published in

1998. Increases in either area under the concentration-time curve (AUC) or maximum plasma concentration (C_{max}) were found with 34 of these, the major mechanism being considered to be inactivation of intestinal cytochrome P450 3A4, a so-called mechanism-based inhibition. Although recent reports point to the inhibitory effects of grapefruit juice on the function of P-glycoprotein, which transports substrates from enterocytes back into the lumen, the contribution to the bioavailability of drugs that are substrates of P-glycoprotein has not been established yet. Dramatic decreases in AUC and C_{max} for two drugs in association with grapefruit juice ingestion has been reported and, in these cases, inhibitory effects on organic anion transporting polypeptide, which mediates absorption from the intestinal lumen to enterocytes, might be involved. Other citrus juices such as Seville (sour) orange juice and commonly ingested varieties of orange juice also showed significant effects on the AUC and C_{max} of some drugs. Although the situation is complex and uncertainties remain, we recommend that patients avoid citrus juice intake while taking medications and that healthcare providers advise against citrus juice intake in this setting until any interactions with subject drugs can be clarified in clinical studies.

It is generally accepted that intake of some foods may affect the pharmacokinetics of drugs. For example, foods containing many metal ions, such as calcium, magnesium, aluminium, iron (milk, milk products, etc.) inhibit the absorption of some antibacterial agents (tetracycline, enoxacin, etc.) because of chelation. Recently, it was reported that St John's wort, one of the world's most popular herbal preparations, can reduce the blood concentrations of some drugs, including warfarin (an anticoagulant), theophylline (a bronchodilator) and oral contraceptives by induction of cytochrome P450 (CYP) 3A4 (the isoform most active in drug metabolism by CYP), CYP2C9, CYP1A2 or P-glycoprotein.[1] Changes in pharmacokinetic parameters, such as area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}) and elimination half-life ($t_{1/2}$) of a drug, resulting from ingestion of combinations of food would depend on the kind and amount of foodstuffs ingested, the drug itself and the timing of administration relative to food intake.

In 1991, the first clinical study of grapefruit juice-drug interaction demonstrated an obvious increase in the AUC and C_{max} of the calcium channel antagonists felodipine and nifedipine.[2] Since then, many studies of grapefruit juice-drug interactions have been conducted and two reviews of this topic were published in 1998.[3,4] The major conclusions were that grapefruit juice increases the AUC and C_{max} of orally coadministered drugs, such as felodipine, nitrendipine and nisoldipine (calcium channel antagonists), ciclosporin (an immunosuppressant), terfenadine (an antihistamine) and midazolam and triazolam (anxiolytics) and that drugs with lower oral bioavailability are affected to a greater degree. The mechanism of action is considered to be inhibition of CYP3A4 in the small intestine, probably as a result of accelerated CYP3A4 degradation, which means that the process is 'mechanism-based' rather than competitive. The effect of grapefruit juice continues for up to 24 hours at least after intake and cumulative effects with time have been observed. On the basis of results from *in vitro* studies, the candidate ingredients in grapefruit juice that are predicted to account for this interaction are naringin (flavonoid) and 6′,7′-dihydroxybergamottin (furanocoumarin). However, when the reviews were conducted in 1998, the candidates for the causative ingredient were still under investigation because clinical investigations, using pure naringin or supernatant and particle fractions of grapefruit juice suggested that neither of these substances would make a major contribution to interactions in humans.

We conducted a literature search of MEDLINE (1998–October 2004) using the keyword 'grapefruit juice' for new and updated information since the

subject of grapefruit juice-drug interaction was last reviewed in 1998[3,4] and found more than 200 reports. Therefore, in this article, we re-evaluate grapefruit juice-drug interactions (mechanisms, kinds of drugs affected, extent of effects and active ingredients). Furthermore, because recent reports have shown interactions between other citrus juices and some drugs, we also summarise these new findings, focusing on active ingredients. Finally, we propose recommendations for patients and healthcare providers in relation to the risks of taking medications close to citrus juice ingestion.

1. Mechanism of Grapefruit Juice-Drug Interactions

Two previous reviews showed that grapefruit juice acts at the absorption stage in the small intestine because of the lack of interaction between grapefruit juice and intravenously administered drugs; reduction of intestinal CYP3A4 activity was considered a possible mechanism (see section 1.1).[3,4] In addition to an effect on CYP3A4, new and updated reports have suggested the involvement of two transporters in the small intestine (see sections 1.2 and 1.3).

1.1 Cytochrome P450 3A4

In previous reviews, a mechanism-based inhibition of intestinal CYP3A4 was cited as the cause of grapefruit juice-drug interactions, based on the finding that CYP3A4 protein content in enterocytes (luminal epithelial cells in the small intestine) was reduced without change in corresponding messenger RNA levels after grapefruit juice ingestion in human volunteers.[5] In mechanism-based inhibition, the inhibitor is metabolically activated by an enzyme and then irreversibly inactivates the same enzyme by covalent binding,[6,7] which means that return of enzyme activity requires *de novo* enzyme synthesis. However, it had been reported in previous reviews[3,4] that some ingredients in grapefruit juice exhibited competitive (reversible) inhibition of CYP3A4 activity *in vitro*. The relative importance of these two different mechanisms in clinical grapefruit juice-drug interactions has yet to be clarified.

Recently, mechanism-based inhibition was also demonstrated in *in vitro* experiments using cell free enzyme assay systems[8-10] and in a human colon carcinoma cell line (Caco-2 cells).[11] In addition, two studies of the active ingredients of grapefruit juice[10,12] (see sections 4.1.1 and 4.1.2) have suggested that, rather than competitive inhibition, a mechanism-based inhibition of intestinal CYP3A4 greatly contributes to grapefruit juice-drug interactions *in vivo*.

1.2 P-Glycoprotein

P-glycoprotein was initially isolated because of its role in multidrug resistance to cancer chemotherapeutic agents. Subsequent studies revealed that this transporter is also involved in the pharmacokinetics of many drugs. P-glycoprotein is expressed in the luminal epithelial cells of tissues that are often associated with drug absorption and disposition, for example, hepatocyte canalicular membrane, renal proximal tubules, the intestinal mucosa and the capillaries of the brain.[13] Therefore, inhibition of P-glycoprotein function at these sites might be expected to increase the oral bioavailability of P-glycoprotein substrate drugs.

An inhibitory effect of grapefruit juice on P-glycoprotein may occur mainly in the intestinal wall because of a lack of grapefruit juice effect on the bioavailability of intravenously administered drugs.[14-17] Recently, *in vitro* studies using Caco-2 cells have clearly shown an inhibitory effect of grapefruit juice on efflux of substrates of P-glycoprotein.[18,19] Because P-glycoprotein and CYP3A4 share many substrates and inhibitors,[20] inhibition of P-glycoprotein function is speculated to augment the grapefruit juice-drug interaction resulting from CYP3A4 inhibition.[20] For example, although ciclosporin is known to be a substrate of both intestinal CYP3A4 and P-glycoprotein, a more significant contribution of intestinal P-glycoprotein to the oral bioavailability of this drug has been demonstrated in kidney transplanted patients.[21] Grapefruit juice was reported to increase the oral bioavailability of ciclosporin (AUC increased by a maximum 40–60%), probably by inhibition of P-glycoprotein because Seville (sour) orange juice (see section 3.2) significantly reduced enterocyte concentrations of CYP3A4 with no influence on ciclosporin disposi-

tion.[22] On the other hand, other studies found that the pharmacokinetic parameters of digoxin (a cardiotonic agent) were not affected[23] or only slightly and not significantly affected by grapefruit juice ingestion in healthy volunteers (1.2-fold and 1.1-fold increase in AUC and C_{max}, respectively).[24] However, although digoxin is a substrate for P-glycoprotein that is minimally metabolised, it is not considered an appropriate probe for evaluating the clinical effect of grapefruit juice on intestinal P-glycoprotein because of its high oral bioavailability (70–80%).[25,26] There is no other information available on the effects of grapefruit juice ingestion on P-glycoprotein function *in vivo*.

1.3 Organic Anion Transporting Polypeptide

Recently, marked reduction of both the AUC and C_{max} of fexofenadine (an antihistamine) and celiprolol (a β_1-adrenoceptor antagonist) by grapefruit juice was reported.[27,28] These studies provided the first indications that the oral bioavailability of drugs can be dramatically reduced by grapefruit juice ingestion. Because both fexofenadine and celiprolol are not metabolised by CYP3A4 but are substrates of P-glycoprotein, it had been expected that their bioavailability would have been increased by grapefruit juice ingestion. Therefore, the involvement of a third mechanism in the interaction between grapefruit juice and drugs has been suggested.

Dresser et al.[27] focused on one intestinal transporter, the organic anion transporting polypeptide (OATP), which assists uptake of drugs on the luminal side of enterocytes, thereby opposing the function of P-glycoprotein. These investigators revealed that grapefruit juice markedly reduces human OATP function *in vitro* at a concentration of 0.5%, while P-glycoprotein function is only slightly and not significantly inhibited even at the 10-fold higher concentration of 5.0%. It is considered that this more potent effect of grapefruit juice on OATP function is responsible for the reduction in the AUC and C_{max} of fexofenadine and celiprolol reported in the previously mentioned clinical studies.[27,28] Based on these findings, Dresser et al.[29] proposed a new model involving OATP for fruit juice-drug interaction in small intestine enterocytes.

2. Effects of Grapefruit Juice on the Concentration-Time Curve and Maximum Concentration of Drugs

Tables I, II and III summarise results for all drugs for which pharmacokinetic clinical studies have reported on grapefruit juice-drug interactions; some previously reviewed data are also included in these tables. Although orange juice was used as a control in some studies as shown in section 3.1, the results of these studies were deleted as much as possible because of reports of interactions between orange juice and drugs (see section 3.1). Since the 1998 reviews,[3,4] 37 drugs have been newly found to interact with grapefruit juice in clinical trials. Most studies were conducted by cross-over design and used approximately ten healthy volunteers, but the amount/concentration of ingested grapefruit juice, the frequency of administration and the timing relative to drug administration were variable. The extent of change in the AUC and C_{max} also varied with different drugs. On the basis of changes in AUC and C_{max}, drugs could be classified into the following three groups: group 1: increase (>30% increase in either AUC or C_{max}); group 2: no change; and group 3: decrease (>20% decrease in either AUC or C_{max}).

2.1 Group 1 Drugs

In table I, increases in the AUC and C_{max} of 34 drugs interacting with grapefruit juice are listed in ascending order of oral bioavailability. Most of these drugs are substrates of CYP3A4. Although the degree of increase in AUC and C_{max} appeared to be reciprocal with the value of bioavailability after oral administration (as in previous reviews), this was not always the case. The major reason for this discrepancy is likely to be related to the degree of first-pass metabolism in the intestinal wall. Differences in the method of grapefruit juice ingestion among clinical studies might also be a factor. However, since some drugs such as diazepam and methylprednisolone showed a greater change in AUC than the maximum expected from the bioavailability, elimination of these drugs from the blood might be reduced by grapefruit juice ingestion although there is no supporting evidence for this at present. Thus, the clinical risk levels associated with taking particular drugs in combination with grapefruit juice are not

Table I. Increases in area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) with grapefruit juice for group 1 drugs (i.e. drugs with >30% increase in either AUC or C_{max}). Data with maximum change in AUC are shown

Study	Drug	Bioavailability (%)	Increase[a]		Study design		
					study population,[b] age (y)	grapefruit juice intake	
			AUC	C_{max}		amount[c] (mL)	timing[d]
Fuhr[4]	Saquinavir	1–4	2.2[e]	2.2[e]	12 men (ND)	300	0, +1
Clifford et al.[30]	Terfenadine	<2	2.5[e]	3.4[e]	6 men (mean 39)	300	−0.5
Ebert et al.[31]	Scopolamine[f]	3–50	1.4[e]	0.94	14 (mean 23)	150	−1.0, −0.25, 0
Lilja et al.[32]	Buspirone[f]	4–5	9.2[e]	4.2[e]	10 (mean 22)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5
Lilja et al.[33]	Simvastatin[f]	<5	16.1[e]	9.4[e]	10 (mean 22)	400	−49, −44, −36, −25, −20, −12, 0, +0.5, +1.5
Kantola et al.[34]	Lovastatin[f]	5	15.3[e]	11.8[e]	10 (mean 23)	400	−49, −44, −36, −25, −20, −12, 0, +0.5, +1.5
Schubert et al.[35]	17β-estradiol	5	1.2[g]	1.3[g]	8 ovariectomised women (45–70)	400	0, 8 hourly to +192
Takanaga et al.[36]	Nisoldipine	5–8	4.1[e]	4.9[e]	8 (mean 23)	200	0
Fuhr et al.[37]	Nimodipine	5–10	1.5[e]	1.2[e]	8 men (23–29)	250	0
Soons et al.[38]	Nitrendipine	5–30	2.3[e]	2.1[e]	9 men (mean 25)	150	−15, −10, −0.25, +5, +10
Fingerova et al.[39]	Progesterone[f]	9	1.3	ND	8 women (postmenopausal)	200	0
Charbit et al.[40]	Halofantrine[f]	10 (highly variable)	2.8[e]	3.2[e]	12 (21–36)	250	−72, −48, −24, −12, 0
Di Marco et al.[41]	Dextromethorphan[f]	10 (rat)	5.4 (bioavailability)		11 (median 32)	200	0
Lilja et al.[42]	Atorvastatin[f]	12	2.5[e]	1.1	12 (mean 22)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5
Edgar et al.[43]	Felodipine	14	3.3[e]	2.9[e]	9 men (mean 44)	400	0
Bailey et al.[3] Munoz et al.[44]	Propafenone	15–25	1.3	1.2	12 men (ND)	250	0
Uno et al.[45]	Nicardipine	15–45	1.6[e]	ND	6 men (27–44)	300	−0.5
Veronese et al.[46]	Midazolam	25–40	6.0[e]	2.7[e]	8 men (ND)	480	−2d, −1d, −1.5, −1.0, −0.5
Ducharme et al.[17]	Ciclosporin	30 (highly variable)	1.6[e]	1.4[e]	10 men (mean 28)	250	0, +2
Fuhr et al.[47]	Verapamil	30–40	1.4[e]	1.6[e]	24 (mean 27)	250	0, +3, +8, +12
Kanazawa et al.[48]	Erythromycin[f]	32	1.5[e]	1.5[e]	6 men (mean 34)	600	−0.5
Desta et al.[49]	Cisapride[f]	40–50	2.6[e]	1.8[e]	10 men (21–31)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5

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Table I. Contd

Study	Drug	Bioavailability (%)	Increase[a]		Study design		
					study population,[b] age (y)	grapefruit juice intake	
			AUC	C_{max}		amount[c] (mL)	timing[d]
Weber et al.[50]	Ethinylestradiol	40–50	1.3[eh]	1.4[eh]	13 women (20–29)	100 200	−1.5, 0 +3, +6, +9, +12
Sigusch et al.[51]	Nifedipine	50–60	2.0[e]	1.9[e]	10 men (mean 26)	200	0, +2, +4, +8, +12
Lilja et al.[52]	Triazolam	60	2.4[e]	1.4[e]	16 (19–28)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5
Hollander et al.[53]	Prednisone	62	1.5	1.4	12 renal transplant patients (mean 28)	150	3 hourly from −7.5 to +22.5
Libersa et al.[54]	Amiodarone[f]	67	1.5[e]	1.8[e]	11 men (mean 24)	300	0, +3, +9
Garg et al.[55]	Carbamazepine[f]	70–85	1.4[e]	1.4[e]	10 inpatients[i] (mean 28)	300	Once daily for 2d[j]
Ozdemir et al.[56]	Diazepam[f]	75	3.2[e]	1.5[e]	8 (mean 34)	250	0
Castro et al.[57]	Praziquantel[f]	>80	1.9[e]	1.6[e]	18 men (mean 29)	250	0
Varis et al.[58]	Methylprednisolone[f]	82–92	1.8[e]	1.3[e]	10 (mean 22)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5
Fuhr et al.[59]	Caffeine	100	1.3[e]	ND	12 (mean 34)	300	−0.5, +6, +12, +18, +24, +30, +36
van Agtmael et al.[60]	Artemether[f]	ND (low)	3.5[e]	2.6	8 men (ND)	700	Once daily for 5d[k]
Lee et al.[61]	Sertraline[f]	ND	1.47[e] (trough serum concentrations)		5 patients[l] (mean 69)	240	−144, −120, −96, −72, −48, −24, 0[m]

a Expressed as ratio to control value.

b Healthy men and women unless otherwise stated.

c Volumes per intake. For double-strength juice, the volumes were doubled.

d Hours relative to drug administration if numerical values only are stated.

e Significant grapefruit juice effects ($p < 0.05$).

f Drugs newly reported to interact with grapefruit juice since the two reviews were published in 1998.[3,4]

g Beverage not containing flavonoids (and, therefore, probably not containing furanocoumarins) given as a control.

h Herbal tea given as a control.

i Patients had received therapy with carbamazepine three times daily for the previous 3–4wk and this treatment was never interrupted during the study.

j Grapefruit juice was given with the morning dose of carbamazepine for 2d and blood samples were collected before the second intake and over a period of 8h after the second intake.

k Grapefruit juice was given with artemether once daily for 5d and blood samples were collected before the fifth intake and over a period of 8h after the fifth intake.

l Patients had received therapy with sertraline once daily in the morning for depression for the previous 6wk or more and this treatment was never interrupted during the study.

m Grapefruit juice was given with sertraline once daily for 7d and blood samples were collected before the morning dose of sertraline for 7d.

ND = no available data.

Table II. Primary metabolic enzyme and oral bioavailability of group 2 drugs (i.e. drugs with no change in area under the concentration-time curve [AUC] or maximum plasma concentration [C_{max}] with grapefruit juice)

Study	Drug	Primary metabolic enzyme	Bioavailability (%)	Study design[a]		
				study population,[b] age (y)	grapefruit juice intake	
					amount[c] (mL)	timing[d]
Ho et al.[62]	Quinine[e]	CYP3A4	88	10 men (19–37)	200[f]	Twice daily for previous 5d, 0
Josefsson et al.[63] Vincent et al.[64]	Amlodipine	CYP3A4	81	12 men (mean 32)	240 200	0 Once daily for the following 8d
Yasui et al.[65]	Alprazolam[e]	CYP3A4	80–100	8 men (mean 31)	200	Three times daily for previous 10d, 0
Min et al.[66]	Quinidine	CYP3A4	70	12 men (mean 23)	240	0
Penzak et al.[67] Shelton et al.[68]	Indinavir[e]	CYP3A4	65	13 (mean 24)	240	Previous evening, 0[g]
Cheng et al.[69]	Clarithromycin[e]	CYP3A4	55	12 (mean 35)	240	0, +2
Vandel et al.[70]	Clomipramine[e]	CYP1A2, CYP3A4	<62	6 depressed inpatients[h] (31–67)	250	0
Yasui et al.[71]	Haloperidol[e]	UDP glucuronyltransferase, CYP3A4	60–65	12 women inpatients[i] (mean 53)	200	Three times daily for 7d[j]
Tassaneeyakul et al.[72]	Omeprazole[e]	CYP2C19, CYP3A4	54	13 (ND)	300	0
Christensen et al.[73] Sigusch et al.[74]	Diltiazem	CYP3A4, CYP2D6	40–50	9 men (ND)	200	0, +2, +4, +8, +12
Jetter et al.[75]	Sildenafil[e]	CYP3A4, CYP2C9	40	24 men (mean 29)	250	−1.0, 0
Vandel et al.[70]	Amitriptyline[e]	CYP1A2, CYP2C19, CYP2D9, CYP3A4	33–62	7 depressed inpatients[k] (30–73)	250	0
Zaidenstein et al.[76]	Losartan[e]	CYP2C9, CYP3A4	33	9 (mean 39)	200	−1.0, immediately before 0
Lane et al.[77] Vandel et al.[78]	Clozapine[e]	CYP1A2, CYP2C19, CYP3A4	27–50	15 inpatients (mean 35)	250	Twice daily for 14d[j]
van Rooij et al.[79]	Acenocoumarol	CYP2C9	>80	12 (ND)	ND	ND
Kumar et al.[80]	Phenytoin[e]	CYP2C9, CYP2C19	ND	10 men (28–55)	300	0
Lilja et al.[42] Fukazawa et al.[81]	Pravastatin[e]	Hydroxylase	20	11 (mean 27)	400	−50, −45, −37, −26, −21, −13, 0, +0.5, +1.5
Becquemont et al.[24] Parker et al.[23]	Digoxin[e]	Not metabolised	70–80	7 (mean 24)	240	−0.5, +4, +10 three times daily for the previous 5d and the following 5d
Banfield et al.[82]	Desloratadine[e]	Not identified (unlikely to be CYP3A4 and CYP2C6)	ND	24 (mean 33)	480	Three times daily for the previous 2d, 0, +2

a The most severe condition with the largest amount and the greatest frequency of grapefruit juice intake was used for this table.

Continued next page

Table II. Contd

b Healthy men and women unless otherwise stated.

c Volumes per intake. For double-strength juice, the volumes were doubled.

d Hours relative to drug administration if numerical values only are stated.

e Drugs newly reported to interact with grapefruit juice since the two reviews were published in 1998.[3,4]

f Orange juice was given as a control. Although a 23% decrease in AUC was observed in combination with 50% grapefruit juice, this was considered to be within the range of dispersion because of the decrease of only 4% observed with 100% grapefruit juice.

g Indinavir was administered every 8h for 1d and once the next morning. Grapefruit juice was given with the last dose on d 1 and with the next morning dose.

h Patients had received therapy with clomipramine.

i Patients had received therapy with haloperidol twice daily for 3–31wk and this treatment was never interrupted during the study.

j Grapefruit juice was given three times (twice with drug administration) daily for 7d and blood samples were collected before the last intake and for 1 week after the last intake.

k Patients had received therapy with amitriptyline.

l After administration of clozapine for 50d, grapefruit juice was coadministered twice daily with each clozapine dose for 14d and trough plasma levels of clozapine were determined.

CYP = cytochrome P450; ND = no available data.

easily estimated because the extent of increase in AUC and C_{max} is variable and the actual effects would depend on the pharmacological activity of the parent drug/metabolite, the drug's safety margin and the type of adverse effects the drug causes. Furthermore, it should be mentioned that most clinical studies were conducted for only short periods and involved small numbers of healthy volunteers, rather than over the long-term with patients requiring drug therapy.

New and/or updated information on the pharmacokinetic and pharmacodynamic changes of group 1 drugs with grapefruit juice ingestion are presented in the following sections.

2.1.1 Buspirone

Buspirone is an anxiolytic agent with an oral bioavailability of only 4%.[87] Because a potent CYP3A4 inhibitor, itraconazole, has been shown to greatly increase the AUC of buspirone,[88] it is considered to be metabolised by this enzyme. Grapefruit juice increased the AUC of buspirone 9.2-fold and the C_{max} 4.2-fold, but a significant increase in pharmacodynamic effects was seen only in relation to subjective overall drug effect.[32] The relatively modest impact of grapefruit juice on buspirone may be explained at least in part by the fact that the intensity of a drug effect is generally proportional to the logarithm of the drug concentration in blood.

2.1.2 HMG-CoA Reductase Inhibitors

Simvastatin, lovastatin and atorvastatin have HMG-CoA reductase inhibitory activity that results in reductions in cholesterol biosynthesis. Rhabdomyolysis is known as a rare but severe adverse effect of these agents.[89] They are metabolised by CYP3A4 and have low oral bioavailability (12% for atorvastatin and ≤5% for simvastatin and lovastatin).[89] A battery of clinical studies[33,34,42] that included intakes of large quantities of grapefruit juice (200mL double-strength grapefruit juice intake three times daily for 3 days and drug administration with the first intake of grapefruit juice on the third day), showed a marked increase in AUC for simvastatin and lovastatin (>10-fold). However, HMG-CoA reductase inhibitory activity increased only 3.6-fold for simvastatin. Although the AUC for atorvastatin increased 2.5-fold, the AUC values for its major metabolites following CYP3A4 metabo-

Table III. Decreases in AUC and C_{max} with grapefruit juice for group 3 drugs (i.e. drugs with >20% decrease in either AUC or C_{max}). Data with maximum change in AUC are shown

Study	Drug	Bioavailability (%)	Decrease[a]		Study design			
					study population,[b] age (y)	grapefruit juice intake		
			AUC	C_{max}		amount[c] (mL)	timing[d] (h)	
Penzak et al.[83]	Itraconazole[e]	30–40	0.57[f]	0.64	11 (mean 28)	480	0, +2.0	
Dresser et al.[27]	Fexofenadine[e]	33	0.33[f]	0.38[f]	10 (19–40)	300	0	
						150	+0.5, +1.0, +1.5, +2.0, +2.5, +3.0	
Demarles et al.[84]	Amprenavir[e]	ND	0.90	0.78	12 (ND)	200	0	
Reif et al.[85]	Etoposide[e]	47–76	0.76	ND	6[g] (median 66)	100	+0.25	
Lilja et al.[28]	Celiprolol[e]	30–70	0.15[f]	0.05[f]	12 (21–23)	200	−50, −45, −37, −26, −21, −13, −1, 0, +4, +10, +22, +27	
Gupta et al.[86]	Theophylline	100	0.75	0.82	10 male (median 31)	300	0	

a Expressed as ratio to control value.
b Healthy men and women unless otherwise stated.
c Volumes per intake. For double-strength juice, the volumes were doubled.
d Hours relative to drug administration.
e Drugs newly reported to interact with grapefruit juice since the two reviews were published in 1998.[3,4]
f Significant grapefruit juice effects ($p < 0.05$).
g Patients had received etoposide for poor prognosis or relapsed small-cell lung cancer. No data available on sexes.

AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; **ND** = no available data.

lism decreased by 15–26%. Because the metabolites of atorvastatin have significant HMG-CoA reductase inhibitory activity, this decrease in the AUC of the metabolites of atorvastatin might lead to a lesser increase in the total activity in blood (1.5-fold for atorvastatin) than might be expected by consideration of the AUC for the atorvastatin. Therefore, the clinical risk arising from concomitant use of grapefruit juice and these drugs is not as large as would be expected from the change in pharmacokinetic parameters of the parent drugs. In other studies, conducted under more actual conditions, it was reported that the AUC of lovastatin increased 1.94-fold (oral dose of lovastatin in the evening after consuming an 8-ounce glass of regular-strength grapefruit juice with breakfast for 3 days),[90] and that of atorvastatin increased 1.40-fold (200mL regular-strength grapefruit juice intake three times daily for 3 days and drug administration with the first intake of grapefruit juice on the third day).[81]

2.1.3 Dextromethorphan

Although there is no information available on the oral bioavailability in humans of dextromethorphan, an over-the-counter and prescribed antitussive agent, it is a substrate of CYP3A4 and CYP2D6. Grapefruit juice increased the bioavailability of dextromethorphan by 5.4-fold, based on analysis of the compound and its metabolites in urinary samples.[41] However, the interaction between grapefruit juice and dextromethorphan would not be as clinically important as expected because metabolites are reported to have the same extent of pharmacodynamic activity as the parent drug.[91]

2.1.4 Amiodarone

Amiodarone, an antiarrhythmic agent, is metabolised by CYP3A4 to the more potent metabolite N-desethylamiodarone. The oral bioavailability of the parent drug is 67%.[89] Administration of amiodarone is known to cause torsade de pointes, a rare but sometimes fatal ventricular arrhythmia, which occurs in the context of QT interval prolongation.[89] This is one of the most serious clinical risks associated with group 1 drugs. Grapefruit juice completely inhibited the production of N-desethylamiodarone, resulting in 50% and 84% increases in the AUC and C_{max} of amiodarone, respectively.[54] As expected from experimental results showing greater

electrophysiological properties of N-desethylamiodarone than those of the parent drug,[92,93] the pharmacodynamic effect (QT prolongation) of concomitant use of grapefruit juice is smaller than that expected from pharmacokinetic studies. In a clinical study, grapefruit juice reduced the prolongation in QT intervals caused by the administration of amiodarone.[54]

2.1.5 Antimalarial Agents

Interactions between antimalarial agents and grapefruit juice have been newly reported since the reviews published in 1998.[3,4] The oral bioavailability of artemether could not be estimated because intravenous administration has not been approved for this agent. Grapefruit juice increased the AUC and C_{max} of artemether by 3.5-fold and 2.6-fold, respectively,[60] but there is no information on pharmacodynamic changes. For halofantrine, torsade de pointes is one of the known adverse effects.[89] With grapefruit juice, a 2- to 3-fold increase in the extent of QT interval prolongation was reported with 2.8-fold and 3.2-fold increases in the AUC and C_{max} of this drug, respectively.[40] Because of concerns about the risk of torsade de pointes, concomitant use of grapefruit juice with halofantrine should be avoided.

2.1.6 Ciclosporin

Ciclosporin, an immunosuppressant, is used in transplant patients and is a substrate of CYP3A4 and P-glycoprotein. It is well known that grapefruit juice significantly increases the AUC and C_{max} of orally administered ciclosporin in renal transplant patients and healthy volunteers, although the extent of these increases is only 40–60% (maximum).[17] Recent reports have provided similar results and shown that grapefruit juice also affects the formation and/or elimination of metabolites M1 and M9.[94-96] Although changes in the AUC and C_{max} of the M1 metabolite were equivocal, reductions in the AUC and C_{max} for the M9 metabolite were consistently observed. The increased systemic exposure to ciclosporin and changes in its metabolites might suggest that metabolic inhibition of ciclosporin by intestinal CYP3A4 could occur in combination with grapefruit juice. However, the major contribution to the increase in the AUC and C_{max} of ciclosporin by grapefruit juice is considered to result from a reduction in P-glycoprotein function (see section 1.2). Although the inhibitory effect of grapefruit juice on P-glycoprotein has clearly been shown *in vitro* (see section 1.2), the change in the AUC of ciclosporin is moderate.[17] However, the consequent effect would not be negligible because of high individual differences in bioavailability, the potential for serious adverse effects (nephrotoxicity, hypertension and cerebral toxicity) and the narrow therapeutic index of ciclosporin.[89]

2.2 Group 2 Drugs

Table II lists 19 drugs for which both the AUC and C_{max} appear not to be affected in combination with grapefruit juice ingestion, together with the primary metabolic enzymes involved with metabolism of these drugs and their oral bioavailabilities. For most drugs in this group, the results of clinical studies are newly reported. The pharmacokinetic parameters of alprazolam (an anxiolytic agent), quinine (an antimalarial agent), quinidine (an antiarrhythmic agent), indinavir (an anti-HIV protease inhibitor), clarithromycin (an antibacterial agent) and amlodipine (a calcium channel antagonist) were not affected by grapefruit juice despite the fact that their primary metabolic enzyme is CYP3A4. Therefore, it is considered that the primary metabolism of these drugs might not occur in the small intestine. The other drugs listed in table II are not metabolised by CYP3A4 or are metabolised by both CYP3A4 and other enzymes. For example, the pharmacokinetic parameters of losartan were barely affected by the CYP3A4 inhibitor itraconazole because losartan is a substrate for both CYP3A4 and CYP2C9.[97,98]

2.3 Group 3 Drugs

Recently, some clinical studies have shown that concomitant intake of grapefruit juice can decrease the AUC and C_{max} of orally coadministered drugs (table III).

For example, values for fexofenadine and celiprolol were markedly lowered when coadministered with grapefruit juice. For fexofenadine, a concentration relationship was detected, i.e. 100% grapefruit juice decreased AUC by approximately 70% whereas 25% diluted grapefruit juice decreased AUC by approximately 20%.[27] Since the metabo-