Role of Human Cytochrome P450 3A4 in Metabolism of Medroxyprogesterone Acetate

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ABSTRACT
Medroxyprogesterone acetate (MPA) is a drug commonly used in endocrine therapy for advanced or recurrent breast cancer and endometrial cancer. The drug is extensively metabolized in the intestinal mucosa and in the liver. Cytochrome P450s (CYPs) involved in the metabolism of MPA were identified by incubation of human liver microsomes and recombinant human CYPs. In this study, the overall metabolism of MPA was determined as the disappearance of the parent drug from an incubation mixture. The disappearance of MPA in human liver microsomes varied 2.6-fold among the 18 samples studied. The disappearance of MPA in the same panel of 18 human liver microsomes was significantly correlated with triazolam α-hydroxylase activity, a marker activity of CYP3A (r = 0.764; P < 0.001). Ketoconazole, an inhibitor of CYP3A4, potently inhibited the disappearance of MPA in 18 human liver microsomes. Anti-CYP3A antibody also inhibited 86% of the disappearance of MPA in human liver microsomes. Although sulfaphenazole (an inhibitor of CYP2C9) and S-mephenytoin (an inhibitor of CYP2C19) partially inhibited the disappearance of MPA, no effect of the anti-CYP2C antibody was observed. The disappearance of MPA did not correlate with either the activity metabolized via CYP2C9 (diclofenac 4′-hydroxylase activity) or the activity metabolized via CYP2C19 (S-mephenytoin 4′-hydroxylase activity). Among the 12 recombinant human CYPs (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) studied, only CYP3A4 showed metabolic activity of MPA. These results suggest that CYP3A4 is mainly involved in the overall metabolism of MPA in human liver microsomes.

INTRODUCTION
MPA2 is a drug commonly used in endocrine therapy for advanced or recurrent breast cancer and endometrial cancer. Although it is controversial whether there is a relationship between the dose of MPA and the response to therapy (1–4), a higher frequency of toxicity has been seen at higher doses (3–4). MPA extensively undergoes first-pass metabolism in the intestinal mucosa and in the liver (5), and the bioavailability of MPA after oral administration is reported to be only approximately 5% (6, 7). In addition, it is known that bioavailability of MPA after oral administration is highly variable, and there is a more than 10-fold difference in the steady-state concentration at the same dose (4, 8).

Much of the variability in the plasma concentration of a drug among patients receiving the same dosage is caused by the marked interindividual variations in oxidative drug metabolism, resulting mostly from variability in the expression of different CYP enzymes in the liver and extrahepatic tissues (9). CYP comprises a large family of hemoprotein (10), and the metabolism of xenobiotics in humans is handled mainly by enzymes from three families: CYP1, CYP2, and CYP3 (11). The structure of MPA is similar to that of progesterone, which is extensively metabolized via 16α-, 6β-, and 2β-hydroxylation by CYP3A4 and via 21-hydroxylation by CYP2C19 (12). MPA is also considered to be a substrate for CYPs (13–15); however, there have been no studies on the identification of enzymes involved in the major metabolic pathway of MPA in humans.

Recently, Suzuki et al. (16) reported that the approach based on the disappearance rate of a parent drug is applicable to the identification of a major isoform(s) of CYP involved in the drug metabolism in human liver microsomes. In this study, we determined the overall metabolism of MPA as the disappearance of the parent drug from an incubation mixture, and we examined the roles of several human CYPs in the metabolism of MPA by using human liver microsomes and microsomes from baculovirus-infected insect cells expressing individual human CYPs.

MATERIALS AND METHODS

Chemicals. MPA was a gift from Pharmacia & Upjohn (Tokyo, Japan), ketoconazole was from Janssen Pharmaceutica (Beerse, Belgium), and prazepam was from Nippon Roche (Tokyo, Japan). Furaphylline, sulfaphenazole, and S-mephenytoin were purchased from Daiichi Pure Chemicals (Tokyo, Japan). SKF-525A was purchased from Research Biochemical

Received 1/1/00; revised 4/25/00; accepted 5/10/00.

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2 The abbreviations used are: MPA, medroxyprogesterone acetate; CYP, cytochrome P450; HPLC, high-performance liquid chromatography; P-gp, P-glycoprotein.
Inc. (Wayland, MA). NADP+, glucose-6-phosphate and glucose-6-phosphate dehydrogenase were purchased from Oriental Yeast (Tokyo, Japan). HPLC-grade acetonitrile and methanol, and analytical-grade aniline hydrochloride, quinidine sodium, coumarin, and other reagents were purchased from Wako Pure Chemical Industries (Osaka, Japan).

Microsomes prepared from baculovirus-infected insect cells expressing CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 were obtained from Gentest (Woburn, MA). All recombinant CYPs were coexpressed with NADPH CYP oxidoreductase (OR). Recombinant CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4 were coexpressed with cytochrome b5. Control microsomes were from insect cells infected with wild-type baculovirus.

Tissue Samples and Preparation of Microsomes. Human liver samples were obtained from Japanese patients undergoing partial hepatectomy for treatment of metastatic liver tumors at the Division of Oncology, Department of Medicine, National Cancer Center Hospital East (Chiba, Japan). All of the patients were informed about the purpose of the study, and informed consent was obtained from each patient. Liver tissues were rapidly frozen in liquid nitrogen immediately after excision and were stored in liquid nitrogen until use. Microsomes from the human livers were prepared as reported previously (17).

Assay with Human Liver Microsomes. The basic incubation mixture contained 0.1 mg/ml of human liver microsomes, 0.1 mM EDTA, 100 mM potassium phosphate buffer (pH 7.4), an NADPH-generating system (0.5 mM NADP+, 2.0 mM glucose-6-phosphate, 1 IU/ml of glucose-6-phosphate dehydrogenase, and 4 mM MgCl2), and 1 mM MPA, in a final volume of 250 μl. MPA was added to the incubation mixture at a final acetonitrile concentration of 1%. The mixture was incubated at 37°C for 30 min. After the reaction was stopped by adding 100 μl of cold acetonitrile, 50 μl of prazepam (0.25 μg/ml in methanol) was added as an internal standard. The mixture was centrifuged at 1700 × g for 20 min, and 100 μl of the supernatant was analyzed by HPLC.

In a preliminary study, the disappearance rates of MPA at 1 μM did not differ from those at 0.5 and 0.25 μM, which indicated that 1 μM is within the range of linearity of the disappearance rates of MPA in human liver microsomes. Therefore, we used 1 μM MPA as the substrate concentration to determine the disappearance rates of MPA throughout the study.

HPLC Conditions. Determinations of MPA were carried out using a HPLC-UV assay method. The HPLC system consisted of an L-7100 pump (Hitachi, Tokyo, Japan), an L-7480 fluorescence detector (Hitachi), a D-7500 integrator (Hitachi), and a CAPCELL PAK C18 UG120 column (4.6 × 250 mm, 5 μm; Shiseido, Tokyo, Japan). The mobile phase consisted of 10 mM phosphate buffer (pH 7.4) with a flow rate of 1.0 ml/min. The eluate was monitored at 287 nm. The mobile phase for 4′-hydroxylation activity consisted of acetonitrile/0.1 mM EDTA, 100 mM potassium phosphate buffer (pH 7.4), and 1 mM MPA, for 30 min, and 100 μl of the supernatant was added as an internal standard. The mixture was centrifuged at 1700 × g for 20 min, and 100 μl of the supernatant was analyzed by HPLC.

In this study, phenacetin (10 μM) was incubated with 0.2 mg/ml microsomal protein for 30 min, coumarin (0.5 μM) was incubated with 0.1 mg/ml microsomal protein for 5 min, diclofenac (10 μM) was incubated with 0.2 mg/ml microsomal protein for 30 min, S-mephenytoin (100 μM) was incubated with 0.1 mg/ml microsomal protein for 60 min, bufuralol (5 μM) was incubated with 0.1 mg/ml microsomal protein for 10 min, chlorzoxazone (20 μM) was incubated with 0.1 mg/ml microsomal protein for 30 min, and triazolam (25 μM) was incubated with 0.2 mg/ml microsomal protein for 15 min. The formed product was determined by the respective HPLC method. Analyses were performed with the HPLC system described above and an L-7480 fluorescence detector (Hitachi). The mobile phase for phenacetin 0-deethylation activity consisted of 50 mM potassium dihydrogen phosphate/acetonitrile (85/15, v/v) with a flow rate of 0.8 ml/min. The eluent was monitored at 224 nm. The mobile phase for coumarin 7-hydroxylase activity consisted of water/methanol/acetic acid (700/300/2, v/v) with a flow rate of 1.0 ml/min. The eluent was monitored fluorometrically (excitation: 340 nm; emission: 456 nm). The mobile phase for diclofenac 4′-hydroxylation activity consisted of 50 mM phosphate buffer (pH 7.0)/acetonitrile (70/30, v/v) with a flow rate of 1.0 ml/min. The eluent was monitored at 282 nm. The mobile phase for S-mephenytoin 4′-hydroxylation activity consisted of 50 mM potassium dihydrogen phosphate/acetonitrile (75/25, v/v) with a flow rate of 1.0 ml/min. The eluent was monitored at 204 nm. The mobile phase for bufuralol 1′-hydroxylation activity consisted of citrate buffer (pH 3.4)/acetonitrile (80/20, v/v) with a flow rate of 1.0 ml/min. The eluent was monitored fluorometrically (excitation: 252 nm; emission: 302 nm). The mobile phase for chlorzoxazone 6-hydroxylation activity consisted of 50 mM potassium dihydrogen phosphate/acetonitrile (70/30, v/v) with a flow rate of 0.8 ml/min. The eluent was monitored at 287 nm. The mobile phase for triazolam α-hydroxylation activity consisted of 10 mM phosphate buffer (pH 7.4)/acetonitrile/methanol (6/3/1, v/v) with a flow rate of 0.8 ml/min. The eluent was monitored at 220 nm.

Chemical Inhibition. The effects of CYP isoform-specific inhibitors or substrates (i.e., compounds able to act as competitive inhibitors) on the disappearance of MPA at 1 μM substrate concentration were investigated using microsomal preparations obtained from a human liver specimen (GHL24). The inhibitors used in this part of the study were 10 μM furafylline (a CYP1A2 inhibitor), 100 μM coumarin (a CYP2A6 substrate), 10 μM sulfaphenazole (a CYP2C9 inhibitor), 500 μM S-mephenytoin (a CYP2C19 substrate), 10 μM quinidine (a CYP3A4 inhibitor), and 1 μM ketoconazole (a CYP3A4 inhibitor). The concentrations of inhibitors or substrates used in the present study were informed consent was obtained from each patient.
Each column human liver microsomes. Data are expressed as percentages of the initial \( \text{S}-\text{hydroxylation (CYP3A4) in human liver microsomes.} \)

The anti-CYP2C antibody used in the present study was previously verified to inhibit corresponding CYP isoforms in human liver microsomes (18–21).

**Immunoinhibition.** The anti-CYP2C antibody used in the present study was previously verified to inhibit \( \text{S}-\text{mephenytoin 4'-hydroxylation (CYP2C19) and tolbutamide hydroxylation (CYP2C9) by more than 90%, whereas it did not inhibit testosterone 6\beta-hydroxylation (CYP3A4) in human liver microsomes (22).} \)

The anti-CYP3A antibody inhibited testosterone \( \text{6\beta-hydroxylation (CYP3A4) by more than 80%, whereas it did not inhibit S-mephenytoin 4'-hydroxylation (CYP2C19) in human liver microsomes (22).} \)

**Assay with Recombinant CYPs.** Microsomes from baculovirus-infected insect cells expressing CYP1A1 (lot 9), CYP1A2 (lot 11), CYP2A6 (lot 2), CYP2B6 (lot 2), CYP2C8 (lot 2), CYP2C9 (lot 4), CYP2C18 (lot 4), CYP2C19 (lot 3), CYP2D6 (lot 13), CYP2E1 (lot 4), CYP3A4 (lot 21), and CYP3A5 (lot 8) were used. The reactions were carried out as described for the human liver microsomal study. To examine the role of individual CYP isoforms involved in the metabolism of MPA, each of the recombinant CYPs (30 pmol of CYP/ml) described above was incubated with 1 \( \mu \text{M MPA} \) for 15 and 30 min at 37°C, according to the procedure recommended by the supplier.

**Data Analysis.** Data represent the mean of duplicate or triplicate measurements for every experiment. Correlation coefficients \( (r) \) were determined by Pearson’s product-moment method. In the present study, the disappearance of MPA in the medium incubated at 37°C with microsomes in the presence of the NADPH-generating system was determined as the percentage of the initial amount of MPA in the medium without incubation.

**RESULTS**

**CYP-dependent Disappearance of MPA.** Preliminary studies indicated that the disappearance of MPA (1 \( \mu \text{M} \)) was linear up to 30-min incubation time when 0.1 mg/ml microsomal protein was used. Thus, the disappearance of MPA in human liver microsomes was determined using a protein concentration of 0.1 mg/ml and an incubation time of 30 min. The disappearance of MPA in human liver microsomes was completely inhibited by SKF-525A (1 \( \mu \text{M} \)), a typical CYP inhibitor (data not shown).

**Correlation Study.** The disappearance of MPA in human liver microsomes varied 2.6-fold (25.6–71.4% of the initial amount) among the 18 samples studied (Fig. 1). A comparison of the disappearance of MPA and CYP isoform-selective catalytic activity in the same panel of 18 human liver microsomes is shown in Table 1. The disappearance of MPA in the 18 human liver microsome preparations at 1 \( \mu \text{M MPA} \) was significantly correlated with triazolam \( \alpha\)-hydroxylase activity at 25 \( \mu \text{M triazolam} (r = 0.764; P < 0.001). \) No other significant correlations were observed between the disappearance of MPA and catalytic activities of phenacetin \( O\)-deethylation \( (r = 0.414), \) coumarin \( 7\)-hydroxylase \( (r = 0.248), \) diclofenac \( 4’\)-hydroxylase \( (r = 0.385), \) \( S\)-mephenytoin \( 4’\)-hydroxylase \( (r = 0.087), \) bufuralol \( 1’\)-hydroxylase \( (r = 0.162), \) or chlorzoxazone \( 6\)-hydroxylase \( (r = 0.375). \)

**Chemical Inhibition Study.** CYP isoform-specific xenobiotic compounds were screened for inhibitory effects on the disappearance of MPA in human liver microsomes (Fig. 2). Ketoconazole (1 \( \mu \text{M} \)) completely inhibited the disappearance of MPA in human liver microsomes. Sulfaphenazole (10 \( \mu \text{M} \)) and \( S\)-mephenytoin (500 \( \mu \text{M} \)) inhibited the disappearance of MPA to 48 and 71% of the control, respectively. The extent of inhibition by furaphylline (10 \( \mu \text{M} \)) or aniline (100 \( \mu \text{M} \)) of the disappearance of MPA was slight (<18%). No effects of coumarin (100 \( \mu \text{M} \)) and quinidine (10 \( \mu \text{M} \)) were observed.

To clarify the contributions of CYP3A to the disappearance of MPA at 1 \( \mu \text{M MPA} \) in individual microsomes of human livers, the effects of 1 \( \mu \text{M} \) ketoconazole on the disappearance of MPA in microsomes from 18 human livers were determined. Ketoconazole completely inhibited the disappearance of MPA in all 18 human liver microsome samples studied (Fig. 3).

**Immunoinhibition Study.** Fig. 4 shows the inhibition of the disappearance of MPA by polyclonal antibodies against CYP3A or CYP2C. The addition of anti-CYP3A IgG reduced the disappearance of MPA by 86% at 2 mg IgG/mg microsomal

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Table 1: Correlation of the disappearance of MPA with CYP isoform-specific activity in 18 human liver microsomes

<table>
<thead>
<tr>
<th>Catalytic activity</th>
<th>CYP</th>
<th>( r )</th>
</tr>
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<tbody>
<tr>
<td>Phenacetin ( O)-deethylation</td>
<td>1A2</td>
<td>0.414</td>
</tr>
<tr>
<td>Coumarin ( 7)-hydroxylolation</td>
<td>2A6</td>
<td>0.248</td>
</tr>
<tr>
<td>Diclofenac ( 4’)-hydroxylolation</td>
<td>2C9</td>
<td>0.385</td>
</tr>
<tr>
<td>( S)-mephenytoin ( 4’)-hydroxylolation</td>
<td>2C19</td>
<td>0.087</td>
</tr>
<tr>
<td>Bufuralol ( 1’)-hydroxylolation</td>
<td>2D6</td>
<td>0.162</td>
</tr>
<tr>
<td>Chlorzoxazone ( 6)-hydroxylolation</td>
<td>2E1</td>
<td>0.375</td>
</tr>
<tr>
<td>Triazolam ( \alpha)-hydroxylolation</td>
<td>3A</td>
<td>0.764*</td>
</tr>
</tbody>
</table>

*\( P < 0.001. \)
Involvement of Human CYP3A4 in Metabolism of MPA

The involvement of human CYP3A4 in the metabolism of MPA was studied by investigating the disappearance of MPA in human liver microsomes. The disappearance of MPA was completely inhibited by 1 mM SKF 525-A. This result suggests that the overall metabolism of MPA in human liver microsomes is a CYP-dependent metabolic process. Accordingly, the roles of human CYPs in the overall metabolism of MPA in human liver microsomes were investigated in this study.

The results of the present study suggest that CYP3A4 is a principal enzyme responsible for the overall metabolism of MPA in human liver microsomes. The supporting evidence can be summarized as follows: (1) the disappearance rates of MPA in a panel of 18 human liver microsomes was significantly correlated with triazolam α-hydroxylase activity, a maker activity for CYP3A (r = 0.764, P < 0.001, Table 1); (2) ketoconazole (1 μM), a potent inhibitor of CYP3A, completely inhibited the disappearance of MPA in human liver microsomes (Figs. 2 and 3); the anti-CYP3A antibody inhibited the disappearance of MPA in human liver microsomes by 86% (Fig. 4); and (4) a significant disappearance of MPA was observed in only cDNA-expressed CYP3A4. Control microsomes and the other recombinant CYPs exhibited no significant activity.

The results of the chemical inhibition study indicated that the extent of inhibition by anti-CYP2C IgG did not differ from that by preimmuno IgG.

Study with cDNA-expressed CYPs. Microsomes from baculovirus-infected insect cells expressing CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 were examined in terms of the abilities of individual CYP proteins to catalyze the metabolism of MPA. As shown in Fig. 5, the disappearance of MPA by incubation with recombinant CYPs was observed in only CYP3A4. Control microsomes and the other recombinant CYPs exhibited no significant activity.

DISCUSSION

The disappearance of MPA in human liver microsomes was completely inhibited by 1 mM SKF 525-A. This result suggests that the overall metabolism of MPA in human liver microsomes is a CYP-dependent metabolic process. Accordingly, the roles of human CYPs in the overall metabolism of MPA in human liver microsomes were investigated in this study.

The results of the present study suggest that CYP3A4 is a principal enzyme responsible for the overall metabolism of MPA in human liver microsomes. The supporting evidence can be summarized as follows: (1) the disappearance rates of MPA in human liver microsomes were investigated in this study.
Effective of MPA in the absence of antibodies. The mixture of microsomes and antibodies was added to the incubation medium containing MPA (1 μM) and other components, and the reaction was carried out as described in “Materials and Methods.” Data are expressed as percentages of the disappearance of MPA in the absence of antibodies. Each point, the mean of duplicate experiments.

Fig. 4 Effect of anti-CYP3A and anti-CYP2C antibodies on the disappearance of MPA in human liver microsomes (GHL24). Human liver microsomes (0.1 mg/ml) were preincubated with various concentrations of anti-CYP3A antibodies (0 –2 mg of IgG/mg of microsomal protein) or anti-CYP2C antibodies (0 –2 mg of IgG/mg of microsomal protein) for 30 min at room temperature. The mixture of microsomes and antibodies was added to the incubation medium containing MPA (1 μM) and other components, and the reaction was carried out as described in “Materials and Methods.” Data are expressed as percentages of the disappearance of MPA in the absence of antibodies. Each point, the mean of duplicate experiments.

Fig. 5 Metabolic activity of MPA in microsomes from baculovirus-infected insect cells expressing individual human CYPs. A substrate (1 μM MPA) was incubated at 37°C for 30 min with microsomes (30 pmol of CYP/ml) from baculovirus-infected insect cells expressing CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Data are expressed as percentages of the initial amount of MPA in the medium without incubation. Each column, the mean ± SD of three or four different experiments.

These results suggest that CYP1A2, CYP2A6, CYP2D6, and CYP2E1 play negligible roles in the overall metabolism of MPA in human liver microsomes.

The present study suggests that the disappearance of MPA in human liver microsomes was attributable to extensive metabolism via CYP3A4. CYP3A4 is the most abundant P450 present both in the liver and in the epithelial cells that line the lumen of the small bowel (23–25). Therefore, the combination of hepatic and intestinal drug metabolism appears to have a large influence on presystemic or first-pass drug metabolism. Previously, it was reported that bioavailability of MPA after oral administration is highly variable, and there is more than a 10-fold difference in the steady-state concentration of MPA at the same dose (4, 8). Because there is a large interindividual variability in the expression of CYP3A4 (23, 24), the interpatient variations in plasma concentration of MPA may be attributable to large differences in metabolic activity of MPA via CYP3A4 during its first-pass metabolism in the intestine and in the liver.

Recently, intestinal P-gp has been recognized to be important in the absorption of many CYP3A substrates (26, 27). P-gp has been shown to be one of the major factors responsible for the resistance of many cancer cells to chemotherapy agents. In the intestine, P-gp is located almost extensively within the brush border on the apical surface of mature enterocytes, where it pumps xenobiotics from the enterocytes back into the intestinal lumen (28). The close cellular location and P-gp and CYP3A4 expression in mature enterocytes and their similar substrate specificity suggest that these two proteins play a significant role in oral bioavailability of drugs. In addition, there is significant interindividual variation in the intestinal expression of P-gp (29). It has also been reported that there is a marked overlap of inhibitors and inducers for P-gp and CYP3A4 (30). Moreover, MPA could bind to P-gp (31). Hence, not only CYP3A4 but also P-gp may contribute to the interpatient variation in bioavailability of MPA after oral administration.

Ohtsu et al. (32) previously reported that patients undergoing combination drug therapy of MPA with phenobarbital or glucocorticoids showed extremely low blood MPA concentrations and that the MPA concentrations were increased after the discontinuation of phenobarbital. Because both barbiturates and glucocorticoids markedly induce the expression of CYP3A (24), the findings of Ohtsu et al. (32) are in good agreement with the present results that show that CYP3A4 is involved in the overall metabolism of MPA. Therefore, MPA would be metabolized more rapidly in patients undergoing combination drug therapy of MPA and CYP3A4 inducers such as glucocorticoids, barbiturates, and rifampin (24).

CYP3A4 plays a major role in drug-metabolism because of its abundance in the liver and intestine and its broad substrate specificity. Numerous clinically important drugs, including erythromycin, cyclosporine, midazolam, nifedipine, quinidine, and terfenadine, are known as substrates of CYP3A4 (24). In addition, it has been reported that CYP3A4 could metabolize some cancer chemotherapeutic agents, including etoposide (33), ifosfamide (34), tamoxifen (35), and vinblastine (36). Many of the drugs metabolized by CYP3A act as competitive inhibitors of CYP3A. At least on a theoretical ground, MPA would be metabolized more slowly in individuals taking drugs that inhibit CYP3A4. However, such a prediction based on an in vitro study coupled with the theoretical drug-drug interaction potentials discussed above may not apply in the in vivo situation and must be confirmed under clinical conditions by a pharmacokinetic study on MPA in patients who undergo MPA therapy concurrently with drugs that are inhibitors of CYP3A4.
In conclusion, the results of the present study using in vitro techniques suggest that the overall metabolism of MPA appears to be mainly catalyzed by CYP3A4 in human liver microsomes. Because there is a large interindividual variability in the expression of CYP3A4 (23, 24), the interpatient variability in the plasma concentration of MPA may be attributable to the variability in metabolic activity of MPA via CYP3A4.

ACKNOWLEDGMENTS

We thank Tomoyoshi Taniguchi (Tsukuba Research Laboratories, Eisai Co.) for the generous donation of antibodies.

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