# 14 Clinical Implications of CYP Induction-Mediated Drug–Drug Interactions

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## 14.1 INTRODUCTION

There are two major concerns with cytochrome P450 (CYP) induction-mediated drug interaction in clinical practice. First, induction may cause a reduction in therapeutic efficacy of comedications. For drugs whose effect is produced primarily by the parent drug, induction would increase the drug's elimination, resulting in lower drug concentrations and decrease the drug's pharmacological effect. Second, induction may create an undesirable imbalance between detoxification and activation as a result of increased formation of reactive metabolites, leading to an increase in the risk of metabolite-induced toxicity. Unlike CYP inhibition, which is an almost immediate response, CYP induction is a slow regulatory process involving gene transcription, replication of RNA, and biosynthesis of protein. Enzyme induction occurs when a drug stimulates the synthesis of more enzyme protein. During CYP induction, it takes time to reach a new steady state level of CYP enzymes as a result of the balance between the rate of biosynthesis and degradation. On the other hand, the induced CYP enzymes return gradually to basal levels via protein degradation after the inducer is discontinued. The purpose of this chapter is to review the effects of CYP induction on pharmacokinetics of drugs and its clinical implications.

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## 14.2 EFFECTS OF CYP INDUCTION ON PHARMACOKINETICS

### 14.2.1 Theoretical Considerations

Although CYP induction can be readily evidenced by direct measurement of the enzyme amount and activity in the liver in animal studies, it is difficult to perform direct assessment of CYP induction *in vivo* in humans by measuring enzyme amount and activity in the liver, because of ethical consideration and practical limitations. A common but indirect way of assessing the effect of CYP induction in clinical settings is the comparison of plasma AUC of a drug before and after coadministration of an inducer. For this reason, it is important to understand the kinetic relationship between enzyme induction and plasma AUC.

If a drug is metabolized exclusively by the liver, the total clearance ($CL_{total}$) of the drug can be considered to be equal to the hepatic clearance ($CL_H$), which can be expressed as Equation 14.1 or Equation 14.2, according to the well-stirred model or parallel-tube model [1]:

$$CL_{total} = CL_H = Q_H \cdot E = (Q_H \cdot f_u \cdot CL_{int})/(Q_H + f_u \cdot CL_{int}) \tag{14.1}$$

$$CL_{total} = CL_H = Q_H \cdot E = Q_H \cdot (1 - e^{-f_u \cdot CL_{int}/Q_H}) \tag{14.2}$$

where $Q_H$ is the hepatic blood flow, $E$ is the hepatic extraction ratio, $CL_{int}$ is the intrinsic clearance, and $f_u$ is the unbound fraction of drug in the blood. Drugs can be further classified as low or high clearance compounds, depending on whether their elimination clearance is enzyme limited or flow limited [1]. Elimination clearance of a drug, which is much less than hepatic blood flow, is termed *enzyme limited*. In contrast, elimination clearance of a drug is termed flow limited when it is equal to or approaching hepatic blood flow.

Following an oral absorption, hepatic bioavailability ($F_H$) can be expressed as Equation 14.3 or Equation 14.4, depending on the well-stirred model or parallel-tube model.

$$F_H = 1 - E = \frac{Q_H}{(Q_H + f_u \cdot CL_{int})} \tag{14.3}$$

$$F_H = 1 - E = e^{-f_u \cdot CL_{int}/Q_H} \tag{14.4}$$

As shown in Equations 14.3 and 14.4, an increase in the $CL_{int}$ as a result of enzyme induction will cause an increase in first-pass metabolism resulting in a decrease in bioavailability. Following an oral administration, the oral $AUC_{po}$ can be expressed as Equation 14.5 or Equation 14.6, according to the well-stirred model or parallel-tube model.

$$AUC_{po} = \frac{F_H \cdot f_a \cdot Dose}{CL_H} = \frac{f_a \cdot Dose}{f_u \cdot CL_{int}} \tag{14.5}$$

$$AUC_{po} = \frac{F_H \cdot f_a \cdot Dose}{CL_H} = f_a Dose \frac{(e^{-f_u \cdot CL_{int}/Q_H})}{Q_H(1 - e^{-f_u \cdot CL_{int}/Q_H})} \tag{14.6}$$

where $f_a$ is the fraction of dose absorbed from the gastrointestinal lumen.

On the other hand, the $AUC_{iv}$ following intravenous administration can be expressed as Equation 14.7 or Equation 14.8.

$$AUC_{iv} = \frac{\text{Dose}}{CL_H} = \frac{\text{Dose}}{\left[\frac{Q_H \cdot f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}\right]} \tag{14.7}$$

$$AUC_{iv} = \frac{\text{Dose}}{CL_H} = \frac{\text{Dose}}{Q_H(1 - e^{-f_u \cdot CL_{int}/Q_H})} \tag{14.8}$$

To illustrate the effect of enzyme induction on the AUCs of drugs after oral and intravenous administration, computer simulations have been carried out for drugs using Equations 14.5–14.8. For simplicity, the fraction ($f_a$) of absorption of drug from intestinal lumen and the unbound fraction of drug in plasma are assumed to remain unchanged during enzyme induction. The hepatic blood flow is assumed to be 1500 mL/min for the simulations. As shown in Figs. 14.1 and 14.2, an increase in $CL_{int}$ of a drug caused by enzyme induction always results in a decrease in AUC of the drug, with the exception of high extraction ratio drugs ($E > 0.9$) after intravenous administration.

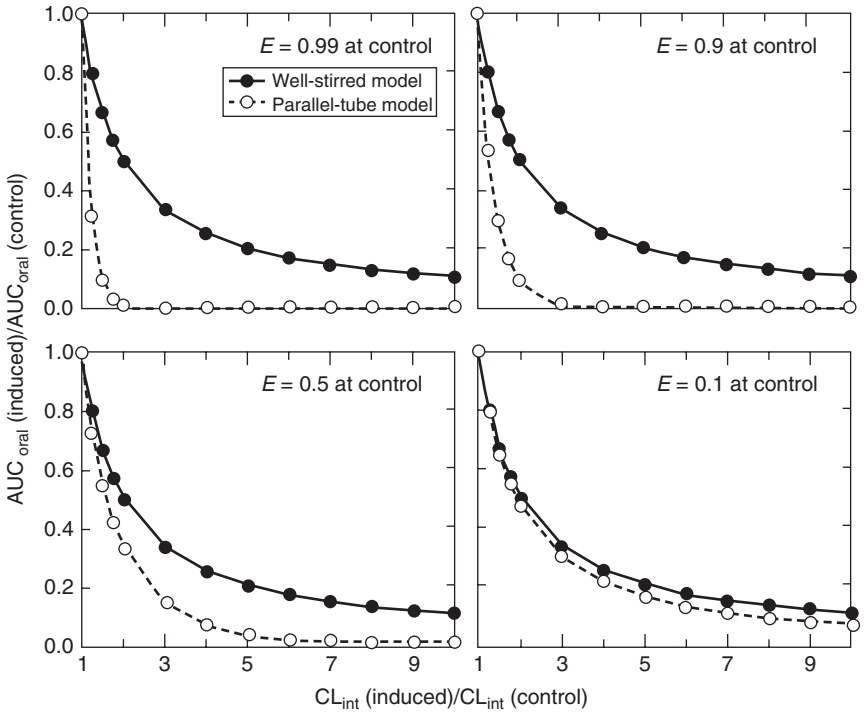


**Figure 14.1** Simulations of effect of enzyme induction on the AUC of drugs after oral administration conducted using Equations 14.5 and 14.6. On the basis of their extraction ratio ($E$), drugs are divided into high clearance ($E > 0.9$), moderate clearance ($E = 0.5$), and low clearance ($E < 0.1$) drugs. For simplicity, the $f_a$ and $f_u$ are assumed to be unchanged during enzyme induction. The hepatic blood flow is assumed to be 1500 mL/min for the simulations.

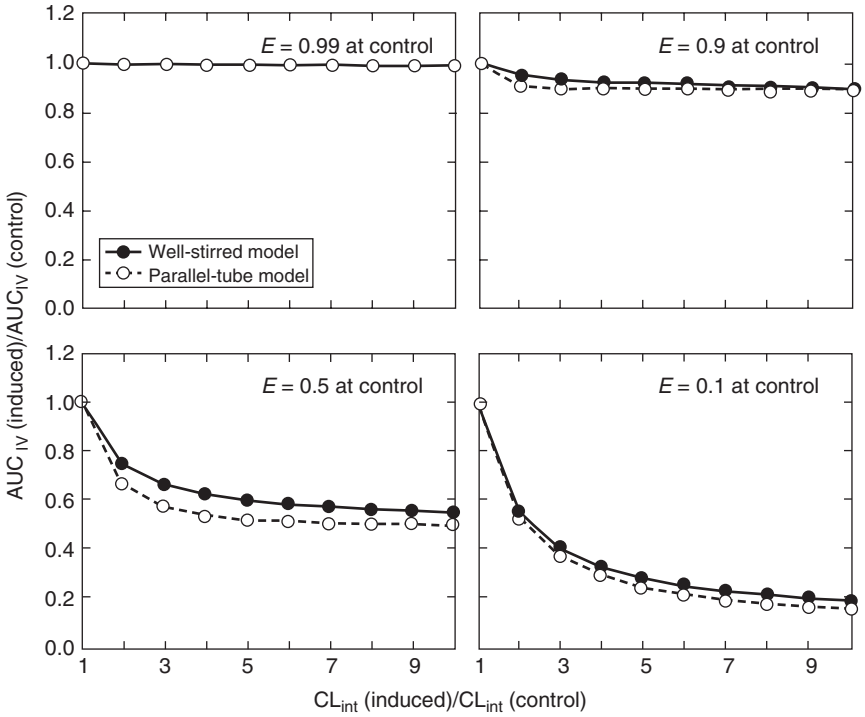


**Figure 14.2** Simulations of effect of enzyme induction on the AUC of drugs after intravenous administration conducted using Equations 14.7 and 14.8. On the basis of their extraction ratio ($E$), drugs are divided into high clearance ($E>0.9$), moderate clearance ($E=0.5$), and low clearance ($E<0.1$) drugs. For simplicity, the $f_a$ and $f_u$ are assumed to be unchanged during enzyme induction. The hepatic blood flow is assumed to be 1500 mL/min for the simulations.

As shown in Fig. 14.1, for low clearance drugs ($E < 0.1$), there is no significant difference in the simulations by either using hepatic well-stirred model or using parallel-tube model. For example, for low clearance drugs ($E<0.1$), a twofold increase in the $CL_{int}$ resulted in a twofold decrease in AUC, independent of hepatic model (well-stirred or parallel-tube model). However, for moderate and high clearance drugs ($E>0.5$), enzyme induction appeared to have more profound effect on the AUC of drug after oral administration when the simulations were conducted using parallel-tube model compared to that using well-stirred model. For example, for high clearance drugs ($E = 0.9$), a 2-fold increase in the $CL_{int}$ resulted in a 10-fold decrease in AUC when hepatic parallel-tube model was used for simulation, whereas a 2-fold increase in the $CL_{int}$ resulted in a 2-fold decrease in AUC when hepatic well-stirred model was used. As discussed later, clinical data of CYP induction-mediated drug interactions appear to support the notion that hepatic parallel-tube model is more appropriate for prediction of CYP induction-mediated drug interaction, particularly for moderate and high clearance compound, following oral administration. This is consistent with the general belief that parallel-tube model is better than well-stirred hepatic model for describing the disposition of moderate and high clearance drugs [1,2].

Following intravenous administration, an increase in the $CL_{int}$ has little effect on the $AUC_{iv}$ of high clearance drugs ($E>0.9$) (Fig. 14.2). As shown in Equations 14.1

and 14.2, when the $CL_{int}$ of a drug is much greater than hepatic blood flow ($Q_H$), the hepatic extraction and clearance are insensitive to changes in $CL_{int}$ of the drug. This is because hepatic blood flow is the rate-limiting step for drug delivery to the liver. Since the elimination clearance of high clearance drugs is hepatic blood flow limited, it is not surprising to see that enzyme induction has little effect on the AUC of high clearance drugs after intravenous administration. On the other hand, the clearance of low clearance ($E = 0.1$) drugs is highly dependent on the enzyme activity. Thus, the clearance of low clearance drug is enzyme limited and sensitive to enzyme induction. As shown in Fig. 14.2, a twofold increase in the $CL_{int}$ resulted in a twofold decrease in AUC of low clearance drugs after intravenous administration. The effect of enzyme induction on the AUC of low clearance drugs after oral dosing is quite similar to that following intravenous administration (Fig. 14.1).

From the above simulations, it becomes evident that the magnitude of AUC reduction caused by enzyme induction is not only dependent on the drug's characteristics, being a low or high clearance compound, but also dependent on the route of administration of the drug.

### 14.2.2 Route-Dependent CYP Induction

The notion that the magnitude of AUC changes caused by CYP induction is highly dependent on the route of drug administration is best exemplified by the case of pentobarbital–alprenolol interaction. Alprenolol, a high hepatic clearance drug with a clearance of 1200 mL/min which is approaching to the hepatic blood flow of 1500 mL/min in humans, is known to be induced by pentobarbital in humans. In a clinical study, alprenolol was administered orally or intravenously to 5 healthy subjects on 2 different occasions before and after 10–14 daily doses of 100 mg pentobarbital [3]. The $AUC_{po}$ of alprenolol after a 200 mg oral dose decreased significantly from an average of 706–154 ng h/mL with barbiturate treatment. In contrast, the $AUC_{iv}$ of alprenolol following an intravenous administration of 5 mg dose only slightly decreased from 67 to 58 ng h/mL with pentobarbital treatment. There was a 458% decrease in the $AUC_{po}$ of alprenolol after oral dosing but only a 15% decrease in the $AUC_{iv}$ of alprenolol after intravenous administration.

The differential effect of route administration has also been reported for another high clearance drug, verapamil, which has a clearance of $> 1000$ mL/min in humans. Treatment with rifampicin had little on the $AUC_{iv}$ of (*S*)- and (*R*)-verapamil after intravenous administration of verapamil, whereas it caused a substantial decrease in the $AUC_{po}$ of (*S*) and (*R*)-verapamil after oral administration of verapamil in humans [4]. After rifampicin treatment for 16 days (600 mg/day), the $AUC_{po}$ of active (*S*)-verapamil decreased from an average of 151 to 5 ng h/mL after oral administration (120 mg), while the $AUC_{iv}$ of (*S*)-verapamil decreased from 77 to 61 ng h/mL following intravenous dosing (10 mg). There is a 3000% decrease in the $AUC_{po}$ of active (*S*)-verapamil after oral administration, while only a 20% decrease in the $AUC_{iv}$ of (*S*)-verapamil following intravenous administration. Similar observations of rifampicin's effects were observed for (*R*)-verapamil after oral and intravenous administration.

Rifampicin also had small effect on the $AUC_{iv}$ of nifedipine, a drug with a clearance of 700 mL/min in humans, after intravenous administration, whereas it greatly reduced the $AUC_{po}$ of nifedipine following oral administration [5]. After seven days of rifampicin treatment (600 mg/day), the $AUC_{po}$ of nifedipine decreased from 280 to

18 ng h/mL when a 20 mg oral dose of nifedipine was given. In contrast, the $AUC_{iv}$ of nifedipine only slightly reduced from 38 to 27 ng h/mL, when the drug was dosed intravenously at 20 μg/kg body weight. There was a 1555% decrease in the $AUC_{po}$ of nifedipin after oral administration, while only a 30% decrease in the $AUC_{iv}$ after intravenous dosing.

From the above examples, it is evident that CYP induction has a little effect on the $AUC_{iv}$ of high clearance drugs after intravenous administration, while it causes a marked decrease in the $AUC_{po}$ of high clearance drugs following oral administration. Kinetically, the $AUC_{iv}$ of a drug after intravenous administration is determined solely by the systemic clearance, as indicated in Equations 14.7 and 14.8. Because the systemic clearance of high clearance drugs is limited by hepatic blood flow, it is insensitive to the changes in enzyme activity. Therefore, for high clearance drugs, an increase of $CL_{int}$ caused by CYP induction will have little effect on the $AUC_{iv}$ after intravenous administration. In contrast, the AUC after oral administration ($AUC_{po}$) is determined by both systemic clearance and bioavailability, as shown in Equations 14.5 and 14.6. Although the systemic clearance is not sensitive to the changes in enzyme activity for high hepatic clearance drugs, their hepatic first-pass metabolism and bioavailability are very sensitive to the changes in enzyme activity.

Unlike high clearance drugs, enzyme induction yields significant effects on the systemic clearance and thereby AUC for low clearance drugs, independent of the route of administration. The systemic clearance of low clearance drugs is enzyme limited and sensitive to the changes in enzyme activity. Because low hepatic clearance drugs are generally not subject to significant first-pass metabolism, both the $AUC_{iv}$ and $AUC_{po}$ are determined mainly by the systemic clearance. Therefore, an increase in the intrinsic clearance caused by CYP induction will have similar magnitude of inductive effect on both the $AUC_{iv}$ and $AUC_{po}$ of the low hepatic clearance drugs. As shown in Figs. 14.1 and 14.2, it is expected that the magnitude of the changes in the AUC of the low clearance drugs will be quantitatively similar between oral and intravenous administration.

The methadone–rifampicin interaction is a good example that both the $AUC_{iv}$ and $AUC_{po}$ of the low clearance drugs are sensitive to the changes of enzyme activity caused by CYP induction. In a study, the effect of rifampicin (600 mg/day for 5 days) on the pharmacokinetics of methadone has been studied with 12 healthy volunteers [6]. Methadone, a low clearance drug (140 mL/min), is used to treat opiate addiction by preventing opiate withdrawal syndrome. After an intravenous dose (4.5 mg), the $AUC_{iv}$ of methadone decreased from an average of 816 ng h/mL before rifampicin treatment to 259 ng h/mL after rifampicin treatment. Similarly, the $AUC_{po}$ of methadone decreased from an average of 1128 ng h/mL before rifampicin treatment to 282 ng h/mL after oral administration of methadone (10 mg). The rifampicin treatment caused a similar magnitude of reduction of methadone AUC after both oral and intravenous administration. There was a 3.2-fold decrease in the $AUC_{iv}$ of methadone after intravenous administration and a 4-fold decrease in the $AUC_{po}$ of methadone after oral administration.

### 14.2.3 Clearance-Dependent CYP Induction

Another intriguing aspect of the effect of CYP induction on the pharmacokinetics of drugs is that the magnitude of AUC reduction caused by enzyme induction is dependent on the drug's characteristics, being a low or high clearance compound.

As shown in Fig. 14.1, the magnitude of $AUC_{po}$ reduction after oral administration appears to be greater for high clearance drugs compared to that for low clearance drugs. Cyclosporine, tacrolimus, methadone, alprazolam, diazepam, zolpidem, and zolpiclone are metabolized mainly by CYP3A4 and are categorized as low clearance drugs because their clearance (<200 mL/min) is much smaller than hepatic blood flow (1500 mL/min). On the other hand, nifedipine, midazolam, triazolam, and indinavir are good substrate for CYP3A4 and are considered as moderate clearance drugs as their clearance is about half of hepatic blood flow, ranging from 400 to 700 mL/min. Verapamil, a good substrate of CYP3A4, has a clearance of 1000 mL/min and is categorized as high clearance drugs. Clinical studies have shown that treatment with rifampicin (a potent CYP3A4 inducer) caused significant but different magnitude of reduction in the $AUC_{po}$ of these drugs. As shown in Table 14.1, the magnitude of the reduction in the $AUC_{po}$ appears to be smaller for the low clearance drugs (3- to 8-fold) than that for moderate clearance drugs (9- to 24-fold) or high clearance drugs (30- to 50-fold) [4–16]. As shown in Table 14.1, high clearance drugs are more sensitive to CYP induction as compared to low clearance drugs. These observations are very similar to the simulations when parallel-tube model, but not well-stirred model, was employed (Fig. 14.1). In other words, simulations by parallel hepatic model, rather than well-stirred model, more accurately reflect the *in vivo* CYP induction-mediated drug–drug interactions.

CYP2C8 and CYP2C9 can also be induced by rifampicin. However, the effect of rifampicin on drugs that are predominately metabolized by CYP2C8 or CYP2C9 appears to be less significant compared to that on drugs metabolized by CYP3A4 (Table 14.2). Rifampicin treatment only caused three- to fourfold changes in the $AUC_{po}$

**TABLE 14.1 Effect of Rifampicin on the Oral AUC of Drugs that are Metabolized Predominately by CYP3A4**

| Drug | Type of Clearance (CL)[a] | Rifampicin (mg/d) | AUC (ng h/mL) | | Fold of Induction[b] | References |
|---|---|---|---|---|---|---|
| | | | Before RIF | After RIF | | |
| Cyclosporine | Low | 600 × 11 d | 8986 | 2399 | 3.7 | 7 |
| Tacrolimus | Low | 600 × 18 d | 351 | 112 | 3.1 | 8 |
| Methadone | Low | 600 × 5 d | 1128 | 262 | 4.3 | 6 |
| Alprazoam | Low | 450 × 4 d | 224 | 28 | 8.0 | 9 |
| Diazepam | Low | 600 × 7 d | 4430 | 1040 | 4.2 | 10 |
| Zolpidem | Low | 600 × 5 d | 1202 | 336 | 3.6 | 11 |
| Zopiclone | Low | 600 × 5 d | 473 | 86 | 5.5 | 12 |
| Quinidine | Moderate | 600 × 7 d | 8000 | 910 | 8.8 | 13 |
| Midazolam | Moderate | 600 × 5 d | 612 | 25 | 24.0 | 14 |
| Triazolam | Moderate | 600 × 5 d | 14.8 | 0.74 | 20.0 | 15 |
| Nifedipine | High | 600 × 7 d | 280 | 18 | 15.5 | 4 |
| Indinavir | High | 600 × 8 d | 18.8[c] | 1.2[c] | 16.0 | 16 |
| *S*-Verapamil | High | 600 × 12 d | 152 | 5 | 30.0 | 4 |
| *R*-Verapamil | High | 600 × 12 d | 724 | 14 | 52.0 | 4 |

*Abbreviation:* RIF, rifampicin.

[a]Type of clearance: low clearance <200 mL/min; moderate clearance >500 mL/min; and high clearance >1000 mL/min.

[b]Fold induction: the ratio of AUC before and after rifampicin treatment.

[c]μg h/mL.

of warfarin, which is metabolized predominately by CYP2C9 [17]. After the treatment with rifampicin at 600 mg twice daily for 4 days, the $AUC_{po}$ of (*R*)-warfarin decreased from an average of 159–47 μg h/mL, while the $AUC_{po}$ of (*S*)-warfarin decreased from 232 to 60 μg h/mL in healthy volunteers receiving an oral dose of racemic warfarin.

Rosiglitazone, an insulin-sensitizing agent, is eliminated mainly by CYP2C8 [22]. After the treatment of rifampicin 600 mg once daily for 6 days in healthy volunteers, the $AUC_{po}$ of rosiglitazone decreased from an average of 2676–988 ng h/mL after an oral administration [18]. Glimepiride is a new sulphonylurea antidiabetic agent, which is eliminated mainly by CYP2C9 [23]. There was only a 1.5-fold decrease in the $AUC_{po}$ of glimepiride after the treatment of rifampicin 600 mg once daily for 5 days [19]. Following an oral administration, the $AUC_{po}$ of glimepiride decreased from 287 ng h/mL before the rifampicin treatment to 190 ng h/mL after the rifampicin treatment. Similarly, rifampicin has lees profound effect on the $AUC_{po}$ of gliclazide, glyburide, and glipizide, which are eliminated predominately via metabolism by CYP2C9 [20,21]. The magnitude of reduction in the $AUC_{po}$ after the rifampicin treatment ranged from 1.3- to 2.9-fold for gliclazide, glyburide, and glipizide (Table 14.2).

All of the CYP2C8/CYP2C9 drugs listed in Table 14.2 can be classified as low hepatic clearance drug because their clearance value is less than 200 mL/min in humans. The relatively small changes in the $AUC_{po}$ of these CYP2C8/CYP2C9 drugs after rifampicin treatment are consistent with the notion that the magnitude of reduction in the $AUC_{po}$ after CYP induction tends to be lower for low hepatic clearance drugs compared to that for high hepatic clearance drugs. However, even for low hepatic clearance drugs, the effect of rifampicin appears to be less significant for CYP2C8/CYP2C9 drugs compared to CYP3A4 drugs. As shown in Tables 14.1 and 14.2, the changes in $AUC_{po}$ were generally smaller for CYP2C8/CYP2C9 drugs (1.3- to 3.5-fold) than that for low clearance drugs of CYP3A4 (3.5- to 8-fold). The differences in the magnitude of $AUC_{po}$ reduction between CYP3A4 drugs and CYP2C8/CYP2C9 drugs may be because of differential induction between different CYP genes by rifampicin, suggesting that the *CYP2C8* and *CYP2C9* genes are less sensitive to rifampicin as compared with *CYP3A4* gene.

**TABLE 14.2 Effect of Rifampicin on the Oral AUC of Drugs that are Metabolized Predominately by CYP2C8 or CYP2C9 in Humans**

| Drug | Type of Clearance (CL)[a] | Rifampicin (mg/d) | AUC (ng h/mL) | | Fold of Induction[b] | References |
|---|---|---|---|---|---|---|
| | | | Before RIF | After RIF | | |
| Rosiglitazone | Low | 600 × 6 d | 2676 | 988 | 2.7 | 18 |
| Glimepiride | Low | 600 × 5 d | 287 | 190 | 1.5 | 19 |
| Gliclazide | Low | 600 × 6 d | 44[c] | 15[c] | 2.9 | 20 |
| Glyburide | Low | 600 × 5 d | 324 | 198 | 1.6 | 21 |
| Glipizide | Low | 600 × 5 d | 801 | 621 | 1.3 | 21 |
| *S*-Warfarin | Low | 600 × 4 d | 220[c] | 59[c] | 3.7 | 17 |
| *R*-Warfarin | Low | 600 × 4 d | 159[c] | 48[c] | 3.3 | 17 |

*Abbreviation:* RIF, rifampicin.

[a]Type of clearance: low clearance <200 mL/min.

[b]Fold induction: the ratio of oral AUC before and after rifampicin treatment.

[c]μg h/mL.

The argument that *CYP2C8* and *CYP2C9* genes are less sensitive to rifampicin is supported by data from *in vitro* studies. In a study with human hepatocytes, the CYP3A4 mRNA increased about 25-fold, while the CYP2C8 and CYP2C9 mRNA only increased 3- to 4-fold after incubation for 24 h with rifampicin [24]. In another study with cultured human hepatocytes, protein and activity of CYP2C8 and CYP2C9 were induced by 3- to 5-fold after rifampicin treatment, while the protein and activity of CYP3A4 was induced by 10-fold after rifampicin treatment [25]. Similar observations of differential induction of CYP genes by rifampicin have been reported by other investigators [26,27].

### 14.2.4 Time- and Dose-Dependent CYP Induction

Enzyme induction is a slow regulatory process, involving gene transcription, replication of RNA, and biosynthesis of protein. Therefore, the CYP induction is expected to be a time- and concentration (dose)-dependent process. The time- and concentration-dependent induction of CYP1A1 and CYP1A2 by tetrachlorodibenzo-*p*-dioxin, (TCDD) has been demonstrated in studies using human splenic lymphocytes and colon carcinoma cell line LS180 [28,29]. In the human splenic lymphocytes and LS180, TCDD markedly induced mRNA, protein, and enzyme activity in a time- and concentration-dependent manner. In the LS180 cell cultures, maximal mRNA induction of CYP1A1 and CYP1A2 occurred between 6 and 24 h after the treatment with TCDD. CYP1A1 protein reached to its maximum at 48 h, while the CYP1A2 protein reached its maximum between 48 and 72 h. These results clearly suggest that there is a lag time between the mRNA translation and protein synthesis, reflecting an extra time required for protein synthesis.

Consistent with *in vitro* observations, time- and dose-dependent TCDD-mediated CYP1A1/2 induction has also been demonstrated in rats *in vivo* [30]. The protein expression of CYP1A1 and CYP1A2 was induced in a dose-dependent manner in rats over a dose range of TCDD (0.01–30 μg/kg). The $ED_{50}$ for TCDD-induced CYP1A1 and CYP1A2 protein expression was estimated to be 0.22 and 0.4 μg/kg, respectively. Although a significant increase in the expression of TCDD-induced CYP1A1 and CYP1A2 protein was observed at 24 h, both CYP1A1 and CYP1A2 reached their maximal levels at 7 days following a single oral dose of TCDD (10 μg/kg). After reaching the peak, the protein level declined slowly via protein degradation. Even at 35 days after a single dose of TCDD administration, CYP1A1 and CYP1A2 protein still did not return to the basal levels. The persistence of the expression of TCDD-induced CYP1A1 and CYP1A2 protein may be related to the slow hepatic elimination of TCDD. Hepatic concentration of TCDD reached a maximum about 8 h after TCDD administration followed by a slow elimination with a half-life of approximately 10 days. A physiologically based pharmacokinetic model incorporated tissue retention of TCDD and its affinity binding to arylhydrocarbon receptor (AhR) has been successfully developed to describe the persistence of CYP1A induction in rats and mice for TCDD and its analogs [31–33].

In addition to TCDD, the time- and dose-dependent induction of CYP1A1 and CYP1A2 by omeprazole has been demonstrated in human hepatoma cell line HepG2 [34,35]. Consistent with *in vitro* observations, dose-dependent induction of CYP1A1/2 caused by omeprazole has also been observed in humans *in vivo*. Induction of intestinal CYP1A by omeprazole was studied in six healthy volunteers [36]. In this study,

endoscopic tissue specimens were analyzed for mRNA and enzyme activity measured by deethylation of ethoxyresorufin before and after the treatment with omeprazole 20 mg/day for 1 week. Large interindividual variations of CYP1A induction were observed. The extent of CYP1A induction ranged from no change in one subject to a sixfold increase in another subject. The individual who did not initially respond (20 mg/day) had a marked increase in both mRNA and enzyme activity after receiving 60 mg of omeprazole daily for 1 week, suggesting that CYP1A induction is dose dependent. Similarly, dose-dependent induction of CYP1A2 by omeprazole has been demonstrated between 40 and 120 mg doses, as measured by $^{13}$C-[*N*-3-methyl]-caffeine breath test [37]. In another clinical study, CYP1A2 was induced in poor metabolizers (PMs) of CYP2C19 but not in extensive metabolizers (EMs) after 7 days treatment with omeprazole at 40 mg/day [38]. Because that omeprazole is eliminated predominately by CYP2C19-mediated metabolism, the plasma $AUC_{po}$ of omeprazole in PMs of CYP2C19 was approximately 5-fold higher than that in EMs after an oral dose of 40 mg. Therefore, the differential effect of omeprazole on CYP1A induction between PMs and EMs of CYP2C19 can be explained by concentration-dependent induction. Collectively, these results clearly demonstrate that omeprazole induces *CYP1A1* and *CYP1A2* genes in a concentration (dose)-dependent manner.

Cigarette smoking is known to induce CYP1A2 enzyme, and the smoking-induced CYP1A2 gradually returns to the basal level via protein degradation after cessation of smoking. In a clinical study, the degradation half-life of the smoking-induced CYP1A2 has been determined in heavy cigarette smokers after cessation of smoking [39]. This study was conducted with 8 men and 4 women who smoked 20 cigarettes or more per day. Subjects were phenotyped for CYP1A2 activity at 6, 4, and 1 days before smoking cessation and at 0, 1, 2, 3, 6, 8, 10, and 13 days thereafter by measuring caffeine clearance. The CYP1A2 activity decreased as a function of time, and a maximal decrease was observed at six or eight days after cessation. The degradation half-life of CYP1A2 activity was estimated to be about 36 h. Similar to the degradation half-life of CYP1A2 enzyme in humans, the degradation half-life of the Aroclor-induced CYP1A1 and CYP1A2 has been estimated to be 20 to 37 h, respectively, in rats [40,41].

Rifampicin is one of the most potent inducers of human *CYP3A4* gene. The time- and dose-dependent induction of CYP3A4 by rifampicin has also been demonstrated in primary cultures of human hepatocytes [42]. In human hepatocytes treated with rifampicin, the induction of CYP3A4 activity (measured by testosterone 6β-hydroxylation) was concentration dependent, and the $EC_{50}$ for rifampicin was estimated to be 0.3–0.5 μM [43]. The dose of rifampicin used in the treatment of tuberculosis is usually between 450 and 600 mg once daily [44]. In a clinical study, the effect of rifampicin on the pharmacokinetics of diazepam (a low hepatic clearance drug) was not significantly different between 600 and 1200 mg oral dose [45]. The $AUC_{po}$ of diazepam decreased from an average of 4430–1040 ng h/mL after the treatment with rifampicin at 600 mg, while from an average of 4170–1130 ng h/mL after 1200 mg rifampicin. Similarly, the effect of rifampicin daily dose of 600, 900, and 1200 mg on the disposition of propranolol (a high hepatic clearance drug) was also not significantly different [46]. Together, these results suggest that the inductive effect of rifampicin at the dosage of 450–600 mg is probably near maximal. The notion of maximal inductive effect at 450–600 mg is further supported by the comparison of the $EC_{50}$ and the systemic exposure of rifampicin at clinical dose. In a clinical study, the peak plasma concentration and $AUC_{po}$ of rifampicin were 20 μg/mL and 100 μg h/mL,

respectively, following an oral dose of 600 mg [47]. The peak concentration (~20 μM) and average systemic exposure (4–5 μM; measured by AUC/24 h) are much greater than the $EC_{50}$ for rifampicin (0.3–0.5 μM).

Time-dependent CYP3A4 induction by rifampicin has also been demonstrated in humans. In a clinical study, the time course of the CYP3A4 induction was evaluated by measuring the steady state trough concentrations of verapamil before, during, and after a 12-day treatment with rifampicin 600 mg once daily [5]. The maximal effect of rifampicin on the CYP3A4 activity was observed at eight days after starting the rifampicin treatment and returned to the baseline activity about two weeks after discontinuing rifampicin treatment. The half-life for increase in CYP3A4 activity was estimated to be about 0.9 day for (*R*)-verapamil and 1.0 day for (*S*)-verapamil, and the half-life for decrease in CYP3A4 activity was 1.5 days for (*R*)-verapamil and 2.1 days for (*S*)-verapamil. It is reasonable to assume that the increase in CYP3A4 activity reflects mainly the synthesis of CYP3A4 protein and the decrease in CYP3A4 activity reflects mainly the degradation of CYP3A4 protein. If the assumption is valid, these results suggest that the process of protein degradation is somewhat slower than the process of protein synthesis.

Consistent with the half-life of CYP3A4 induction of approximately 1 day, a significant CYP3A4 induction was observed as early as 8 h after a single dose of rifampicin [48]. Nifedipine was given orally 8 h after a single dose of rifampicin (1200 mg) in healthy volunteers. The $AUC_{po}$ of nifedipine decreased from an average of 573 ng h/mL before rifampicin treatment to 205 ng h/mL at 8 h after a single rifampicin treatment. Although the change in the $AUC_{po}$ of nifedipine after 8 h (2.8-fold) after a single dose is much less than that after a seven days treatment (15.5-fold as shown in Table 14.1), a duration of 8 h is sufficient to induce a significant amount of CYP3A4 protein level leading to a significant increase in the activity of this enzyme.

## 14.3 EFFECTS OF CYP INDUCTION ON PHARMACODYNAMICS

For drugs whose elimination is cleared primarily by CYP-mediated metabolism, CYP induction will reduce the therapeutic efficacy as a result of a decrease of systemic exposure. In some cases, changes in drug dosage are required in order to attain and maintain a therapy during the initiation, maintenance, and discontinuation of the coadministration of a potent CYP inducer. In addition, CYP induction may create an undesirable imbalance between bioactivation and detoxification, leading to an increase in metabolite-induced toxicity. Although the research on the potential risk of CYP induction-mediated toxicity has received much less attention than the pharmacokinetic and pharmacological effects, there is increasing evidence that CYP induction could be a serious cause for drug-induced toxicity.

### 14.3.1 Effects of CYP Induction on Therapeutic Efficacy

Reduction in therapeutic efficacy caused by CYP induction is best exemplified by the rifampicin–cyclosporine interaction. Because of the treatment with immunosuppressive agents, there is a high incidence of tuberculosis among organ transplant recipients. In a retrospective study, analysis of the records of 880 renal transplant recipients in Turkey revealed that 36 patients were infected and developed tuberculosis after renal

transplantation [49]. In another study, a very high incidence of tuberculosis (42%) was reported among 305 renal transplant recipients in India [50]. Because rifampicin still remains as an effective antituberculosis agent, it is often concomitantly used with cyclosporine (or tacrolimus) in transplant recipients, and clinically significant drug interactions between rifampicin and cyclosporine have been reported. In a clinical study, treatment with rifampicin 600 mg once daily for 11 days caused a more than 3-fold decrease in the $AUC_{po}$ of cyclosporine, presumably due to CYP3A4 induction [7]. Importantly, treatment with rifampicin had caused acute transplant rejection in patients treated with cyclosporine [51]. The acute transplant rejection is most likely because of significant reduction of cyclosporine exposure caused by rifampicin-mediated CYP3A4 induction. Similar to cyclosporine, an 18-day treatment with rifampicin 600 mg daily markedly reduced the $AUC_{po}$ of tacrolimus (a good substrate of CYP3A4) by about 3-fold in patients [8]. Therefore, an increase in the tacrolimus dosage was required to attain the effective blood concentration of tacrolimus in order to avoid graft rejection in transplant recipients [52].

Warfarin–rifampicin interaction is also a good example for CYP induction-mediated reduction of drug efficacy. Warfarin, a prototypic CYP2C9 substrate, remains as the first line anticoagulant therapy. The unfavorable narrow range of therapeutic concentration makes warfarin prone to potentially life-threatening drug–drug interactions [53]. In a clinical study, the $AUC_{po}$ of warfarin was decreased by about 3-fold after a 21-day treatment with rifampicin 600 mg daily [54]. The reduction of warfarin plasma concentration is believed to be due to the rifampicin-mediated CYP2C9 induction. Consistent with a threefold decrease in warfarin plasma concentration, rifampicin treatment caused a threefold decrease in the anticoagulant effect of warfarin. In a case report [55], a patient receiving concomitant rifampicin and warfarin to treat a mycobacterial infection and intraventricular thrombus, respectively, required a more than twofold increase in the dosage of warfarin to attain the therapeutic efficacy, measuring by international normalized ratio (INR). Because of temporal changes of enzyme level, the dose of warfarin should be reduced gradually after discontinuing rifampicin treatment to maintain a balance between therapeutic efficacy and adverse effect. A gradual 70% reduction in warfarin dosage over 4–5 weeks was necessary to maintain the therapeutic INR after rifampicin discontinuation [55]. In another case report, a 72-year-old patient taking warfarin was concurrently administered rifampicin for several months [56]. During this period, satisfactory anticoagulation was achieved only when a high dose of warfarin (20 mg) was given. After discontinuation of rifampicin therapy, warfarin dose was adjusted gradually, until the stabilization of the prothrombin time at warfarin 7.5 mg.

Because of narrow therapeutic index of antiarrhythmic agents, potential interaction with other drugs is of therapeutic importance in the clinical practice. Quinidine, a substrate of CYP3A4, is used for the treatment of cardiac arrhythmias. After 7 days of daily treatment with rifampicin 600 mg in 6 healthy volunteers, the $AUC_{po}$ of quinidine decreased dramatically by 9-fold [13]. In another clinical study, a 7-day treatment with rifampicin 600 mg daily caused a 5-fold decrease in the $AUC_{po}$ of quinidine [57]. Although no published studies or case reports have described the pharmacodynamic changes with respect to the quinidine–rifampicin interaction, it is likely that the interaction could be clinically significant. A clinically significant reduction in the QRS prolongation has been reported as a result of rifampicin–propafenone interaction. Propafenone, a sodium channel-blocking antiarrhythmic drug, is metabolized by CYP2D6 to 5-hydroxy-propafenone and by CYP3A4 to N-dealkylation metabolite

[58]. Both 5-hydroxy-propafenone and N-dealkylation-propafenone are active metabolites with activity as potent as the parent drug. The oxidative metabolites are subsequently eliminated by phase II metabolism, glucuronidation, and sulfation. The effect of rifampicin on the pharmacokinetics and pharmacodynamics of propafenone was studied in six EMs and six PMs of CYP2D6 [59]. After a 9-day rifampicin treatment (600 mg/day), the $AUC_{po}$ of propafenone decreased from an average of 6.9–1.8 μM h in the EMs and from 54 to 16 μM h in PMs. Interestingly, rifampicin also affected the pharmacodynamics of propafenone in both EMs and PMs of CYP2D6. The maximum QRS prolongation decreased from 21% to 13% in EMs and from 15% to 9% in PMs. Since CYP2D6 is not inducible, the rifampicin's effect on the pharmacokinetic and pharmacodynamics of propafenone is probably due mainly to the CYP3A4 induction. However, interpretation of clinical consequences of propafenone by CYP induction would be somewhat complicated in this case because of the formation of active metabolites.

Similarly, the interaction between rifampicin and codeine is quite complex. Codeine is a widely used opiate analgesic agent that is converted through O-demethylation to morphine by CYP2D6 in humans [60,61]. Although the formation of morphine accounts for >10% of over all clearance of codeine, morphine is responsible for most of the analgesic effect of codeine. Unlike morphine which is eliminated mainly by UDP-glucuronosyltransferases (UGTs), codeine is metabolized by multiple enzyme systems, including CYP2D6, CYP3A4, and UGTs [62,63]. The effect of rifampicin on the pharmacokinetics and pharmacodynamics of codeine has been studied in EMs and PMs of CYP2D6 [63]. After treatment of rifampicin (600 mg/day) for 3 weeks, rifampicin had little effect on pharmacodynamics of codeine in PMs of CYP2D6. Because CYP2D6 is not inducible by rifampicin, it is expected that rifampicin will have no significant effect on the pharmacodynamics of codeine in EMs as well. Surprisingly, the codeine's pharmacodynamic effects were attenuated in EMs of CYP2D6 after rifampicin treatment. This is because that rifampicin significantly decreased the concentration of codeine through an increase in the clearance of the major elimination pathways of codeine, namely, CYP3A4-dependent N-demethylation and UGT-dependent glucuronidation, which can be induced by rifampicin. Thus, the conversion of morphine from codeine was significantly reduced in the EMs of CYP2D6 due to the decreased codeine concentration during rifampicin treatment. In addition to the decreased morphine formation, the elimination of the converted morphine can also be enhanced via glucuronidation by rifampicin-induced UGTs.

Morphine is eliminated exclusively by UGTs to form glucuronide-3-morphine and glucuronide-6-morphine in humans [64]. A significant drug interaction has been observed between morphine and rifampicin. In a clinical study, the serum concentrations of morphine, glucuronide-3-morphine, and glucuronide-6-morphine were measured before and after the treatment with rifampicin 600 mg once daily for 13 days [65]. There was only a moderate decrease in the serum concentrations of morphine after the treatment with rifampicin. The $AUC_{po}$ and $C_{max}$ of morphine, respectively, decreased from an average of 132 nM h and 34.5 nM before rifampicin treatment to 97 nM h and 18 nM after rifampicin treatment. Similarly, there was also a significant decrease in the AUC of glucuronide-3-morphine and glucuronide-6-morphine [65]. Although rifampicin treatment only caused a moderate decrease in concentrations of morphine and its active metabolite, a complete loss of analgesic effect of morphine was observed in these volunteers after the treatment of rifampicin.

The HIV protease inhibitors are used for the treatment of patients infected with HIV. Because of the increasing incidence of tuberculosis among patients infected with HIV, rifampicin is often concomitantly used with HIV protease inhibitors. Therefore, rifampicin-mediated CYP induction becomes a serious concern in the treatment of HIV infection [66]. After a 14-day rifampicin treatment (600 mg/day), both the $AUC_{po}$ and $C_{max}$ of saquinavir decreased by more than 4-fold in healthy volunteers [67]. Similarly, treatment with rifampicin (600 mg/day) for 7 days caused a 5-fold decrease in both the $AUC_{po}$ and $C_{max}$ of nelfinavir [68]. Significant reduction in the $AUC_{po}$ and $C_{max}$ of ritonavir and indinavir after the rifampicin treatment has also been reported [16,69]. Because the antiretroviral effect is highly dependent on the systemic exposures of the HIV protease inhibitors, the use of rifampicin is contraindicated to avoid treatment failure. In some cases, a dosage adjustment may be required to achieve the antiretroviral effect. For example, the dosage of efavirenz, a nonnucleotide transcriptase inhibitor, needs to be adjusted from 400 to 800 mg daily, when rifampicin is concurrently administered [70]. Interestingly, efavirenz is also a CYP3A4 inducer. In a clinical study, the $AUC_{po}$ of indinavir was decreased by 35% when coadministered with efavirenz [71]. To compensate the efavirenz-mediated induction, the dosage of indinavir was suggested to increase from 800 mg 3 times daily to 1000 mg 3 times daily.

The effect of rifampicin on the CNS drug action has also been studied. A 5-day rifampicin treatment (600 mg/day) caused a more than 3-fold decrease in the $AUC_{po}$ of zolpidem [11]. In parallel, a significant reduction in the effects of zolpidem was seen in all psychomotor tests (digit symbol substitution, critical flicker fusion test, and Maddox wing test). In another clinical study, rifampicin treatment at 600 mg daily for 5 days resulted in a 5.5-fold decreases in the $AUC_{po}$ of zopiclone and a significant reduction in the hypnotic effects [12]. Similarly, a 5-day rifampicin treatment (600 mg/day) caused a 10- to 20-fold decrease in the $AUC_{po}$ of midazolam and triazolam [14,15]. As a result of the substantial decrease in systemic exposure, both midazolam and triazolam are ineffective in patients taking rifampicin. Therefore, it is advisable to use hypnotic agents that are not predominantly metabolized by CYP3A4 during treatment with rifampicin.

### 14.3.2 Effects of CYP Induction on Drug-Induced Toxicity

Epidemiological and animal studies have suggested that many xenobiotics and drugs cause toxicity by generating reactive metabolites or reactive oxygen species [72–74]. CYP1A enzymes are known to be responsible for metabolic activation and detoxification of some xenobiotics, such as polycyclic aromatic hydrocarbons. Although it is highly controversial whether CYP1A induction is beneficial because of detoxification, or is detrimental because of metabolic activation forming reactive metabolites, there is increasing evidence that CYP1A induction could be a risk factor that may cause toxicity and cancer [75–77]. For example, cigarette smoking has been found to be associated with pulmonary and cardiovascular diseases and cancer via CYP1A induction [78–81]. Recently, *in vitro* and animal studies suggest that some xenobiotics exert their toxicity, not only by generating reactive metabolites but also by altering expression of specific genes through AhR activation [74,75].

Induction of CYP2E1 by ethanol is believed to be responsible for hepatotoxicity by generating oxidative stress species [82,83]. Rate of the formation of superoxide and hydrogen peroxide was significantly increased in microsomes from ethanol-treated rats, in which CYP2E1 was induced [84,85]. *In vitro* studies revealed that human CYP2E1 is

also capable of forming reactive oxygen intermediates and catalyzing lipid peroxidation in CYP2E1-expressed HepG2 cells [86]. There is an increasing body of evidence that ethanol-induced hepatotoxicity is linked to the increased production of oxidative stress species. For instance, the ethanol-induced hepatotoxicity has been shown to correlate with the expression levels of CYP2E1 as well as the elevated lipid peroxidation in rats [87]. Furthermore, treatment of diallylsulfide, an inhibitor of CYP2E1, prevented the elevation of lipid peroxidation and partially blocked the ethanol-induced hepatotoxicity. Similarly, anti-CYP2E1 IgG has been used to prevent the formation of reactive oxygen species after ethanol treatment in animals [88].

Hepatotoxicity caused by CYP2E1 induction in humans has been suggested [89]. A male subject was in the habit of consuming three glass of wine regularly with dinner. He stopped ingesting ethanol when he contracted influenza and began taking acetaminophen for treatment. Several days later, he had a complete liver failure. It is believed that the hepatotoxicity is due to an increased formation of reactive metabolite of acetaminophen, *N*-acetyl-*p*-benzoquinone imine (NAPQI) as a result of CYP2E1 induction caused by heavy alcohol drinking. *In vitro* studies with human liver microsomes have demonstrated that CYP2E1 can modulate the formation of NAPQI [90]. Interestingly, ethanol is able not only to induce but also to inhibit CYP2E1 activity [91]. On the basis of the dual effects of ethanol, Slattery *et al*. [89] have developed a kinetic model to explain the complex ethanol–acetaminophen interaction. Through the model simulations, it becomes clear that the time interval between the last consumption of alcohol and ingestion of acetaminophen is very important in terms of the risk of hepatotoxicity. If acetaminophen is taken in the morning because of a headache as a result of the heavy drinking the night before, there is a high risk of hepatotoxicity. This is because at the next morning after heavy drinking, the low level of ethanol concentration is insufficient to inhibit the formation of NAPQI in the liver where CYP2E1 enzyme activity was induced, resulting in an increased formation of the toxic metabolite. However, if acetaminophen and ethanol are taken together at the same time, the formation of NAPQI is not expected to increase because of the opposite effects of CYP2E1 inhibition and induction by ethanol.

In addition to CYP2E1, NAPQI can also be formed by human CYP1A2 and CYP3A4 [91,92]. Therefore, it has been suggested that CYP1A2 and CYP3A4 may also contribute to the acetaminophen-induced hepatotoxicity. The role of CYP1A2 in acetaminophen-induced hepatotoxicity has been studied in wild-type, *Cyp2e1* $^{(-/-)}$, and *Cyp1a2* $^{(-/-)}$ mice [93–95]. Following the administration of acetaminophen at 250 mg/kg, there was no significant differences in the severity of hepatoxicity between *Cyp1a2* $^{(+/+)}$ and *Cyp1a2* $^{(-/-)}$ mice, as measured by serum alanine aminotransferase. In addition, there was no difference in the urinary metabolites excreted over a 24-h period, including those derived from glutathione (GSH) conjugation of the major reactive metabolite NAPQI of acetaminophen, between the *Cyp1a2* $^{(+/+)}$ and *Cyp1a2* $^{(-/-)}$ mice. With these results, the investigators concluded that CYP1A2 does not play a significant role in acetaminophen hepatotoxicity in mice. Consistent with the findings in mice, induction of human CYP1A2 appears to have little effect on the formation of the reactive metabolite NAPQI of acetaminophen. In a clinical study with EMs and PMs of CYP2C19, omeprazole was administered orally at 40 mg daily for 7 days [96]. A significant CYP1A2 induction was observed only in the PMs but not in EMs of CYP2C19. Despite induction of CYP1A2 activity in the PMs, there was no significant difference in the formation of thioether conjugates,

which are terminal metabolites of NAPQI. Therefore, CYP1A2 induction may not significantly contribute to the formation of NAPQI of acetaminophen.

The role of CYP3A enzymes in acetaminophen-induced hepatotoxicity has also been studied in pregnane X receptor (PXR)-null mice [97]. Pretreatment with pregnenolone-16α-carbonitrile (PCN), a potent inducer of mice Cyp3a11, markedly enhanced acetaminophen-induced hepatotoxicity, as revealed by increased serum concentration of liver enzymes and hepatic centrilobular necrosis in wild-type mice but not in PXR-null mice following an intraperitoneal dose of acetaminophen (350 mg/kg). Furthermore, PCN treatment significantly increased the GSH-derived metabolites of NAPQI in wild-type mice but not in PXR-null mice. These results suggest that Cyp3a11 plays an important role in acetaminophen-induced hepatotoxicity in mice.

The role of CYP3A4 in acetaminophen-induced hepatotoxicity has also been studied in humans. In a clinical study, pretreatment with rifampicin (600 mg/day) for a week showed no effect on the urine recovery of thiol metabolites formed by conjugation of NAPQI with GSH, suggesting that the contribution of CYP3A4 to the formation of NAPQI of acetaminophen may be negligible in humans [98]. On the other hand, the urine recovery of the thiol metabolites formed by conjugation of NAPQI with GSH was decreased by 69%, and the formation clearance of NAPQI was decreased by 74% by pretreatment with disulfiram, a potent CYP2E1 inhibitor [98]. These results strongly suggest that CYP2E1, rather than CYP3A4, is the major enzyme responsible for the acetaminophen-induced hepatotoxicity in humans.

## 14.4 CONCLUSIONS

Although our understanding of CYP induction has advanced significantly over the past 10 years through the discovery of key nuclear receptors, much still remains to be learned about the molecular mechanisms of CYP induction. One of the unsolved issues is the wide interindividual variability in CYP induction. There are a large number of factors that could contribute to the variability, including genetic and environmental variables. The relative contribution between the genetic and environmental variables is not readily assessed due in part to the complexity of CYP induction and insufficiency of proper experimental tools. Another critical issue that may complicate the prediction and interpretation of CYP induction is the interplay between efflux transporters and CYP enzymes. Although there is now an increasing evidence to suggest the interplay between CYPs and efflux transporters because of a striking overlap in substrates and inducers with CYP enzymes and efflux transporters, our knowledge about this interplay is still very limited [99–102]. This is because it is very difficult to accurately estimate the relative contribution of CYP enzymes and transporters to drug absorption and disposition. This is particularly true for drug interactions that are caused by CYP and transporter induction.

Because of the complexity of the contributing factors, quantitative prediction of CYP induction is very difficult, if not impossible. Although numerous *in vitro* systems have been developed to assess CYP induction, these systems are only useful for semiquantitative assessment whether a new drug candidate has a potential for CYP induction. Information obtained from *in vitro* induction studies is still limited in its ability to predict whether there is a "probability" of induction-based drug interactions. If the *in vitro* data suggest that a drug candidate could have a potential for CYP induction,

clinical studies should be conducted earlier to assess the degree of induction. Therefore, the induction data obtained from *in vitro* systems should not serve as a "no-gos" decision for drug development without a proper clinical assessment. Finally, a point worth mentioning is that in many cases, the CYP induction-mediated drug interaction is manageable by adjusting dosage regimen.

## REFERENCES


1. Wilkinson GR. Clearance approaches in pharmacology. Pharmacol Rev 1987;39:1–47.
2. Naritomi Y, Terashita S, Kimura S, *et al*. Prediction of human hepatic clearance from *in vivo* animal experiments and *in vitro* metabolic studies with liver microsomes from animals and humans. Drug Metab Dispos 2001;29:1316–1324.
3. Alvan G, Piafsky K, Linda M, *et al*. Effect of pentobarbital on the disposition of alprenolol. Clin Pharmacol Ther 1977;22:316–321.
4. Fromm MF, Busse D, Kroemer HK, *et al*. Differential induction of prehepatic and hepatic metabolism of verapamil by rifampin. Hepatology 1996;24:796–801.
5. Holtbecker N, Fromm MF, Kroemer HK, *et al*. The nifedipin-rifampin interaction: evidence for induction of gut wall metabolism. Drug Metab Dispos 1996;24:1121–1123.
6. Kharasch ED, Hoffer C, Whittington D, *et al*. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. Clin Pharmacol Ther 2004;76:250–269.
7. Hebert MF, Roberts JP, Prueksaritanont T, *et al*. Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. Clin Pharmacol Ther 1992;52:453–457.
8. Hebert MF, Fisher RM, Marsh CL, *et al*. Effects of rifampin on tacrolimus in healthy volunteers. J Clin Pharmacol 1999;39:91–96.
9. Schmider J, Brockmoller J, Arold G, *et al*. Simultaneous assessment of CYP3A4 and CYP1A2 activity *in vivo* with alprazolam and caffeine. Pharmacogenetics 1999;9:725–734.
10. Ohnhaus EE, Brockmeyer N, Dylewiez P, *et al*. The effect of antipyrine and rifampin on the metabolism of diazepam. Clin Pharmacol Ther 1987;42:148–156.
11. Villikka K, Kivisto K, Luurila H, *et al*. Rifampin reduces plasma concentrations and effects of zolpidem. Clin Pharmacol Ther 1997;62:629–634.
12. Villikka K, Kivisto K, Lamberg TS, *et al*. Concentrations and effects of zopiclone are greatly reduced by rifampicin. Br Clin Pharmacol 1997;43:471–474.
13. Damkier P, Hansen LL, Brosen K. Rifampicin treatment greatly increases the apparent oral clearance of quinidine. Pharmacol Toxicol 1999;85:257–262.
14. Backman JT, Plkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther 1996;59:7–13.
15. Villikka K, Kivisto K, Backman JT, *et al*. Triazolam is ineffective in patients taking rifampin. Clin Pharmacol Ther 1997;61:8–14.
16. Crixivan® package insert. Pennsylvania: Merck & Co; 1997.
17. Heimark LD, Gibaldi M, Tragger WF, *et al*. The mechanism of the warfarin-rifampin drug interaction in humans. Clin Pharmacol Ther 1987;42:388–394.
18. Park JY, Kim KA, Kang MH, *et al*. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. Clin Pharmcol Ther 2004;75:157–162.
19. Niemi M, Kivisto KT, Backman JT, *et al*. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. Br J Clin Pharmacol 2000;50:591–595.
20. Park JY, Kim KA, Park PW, *et al*. Effect of rifampin on the pharmacokinetics and pharmacodynamics of gliclazide. Clin Pharmacol Ther 2003;74:334–340.

21. Niemi M, Backman JT, Neuvonen M, *et al*. Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. Clin Pharmacol Ther 2001;69:400–406.
22. Baldwin SJ, Clarke SE, Chenery RJ. Characterization of the cytochrome P450 enzymes involved in the *in vitro* metabolism of rosiglitazone. Br J Clin Pharmacol 1999;48:424–432.
23. Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type-2 diabetes mellitus. Drugs 1998;55:563–584.
24. Dvorak Z, Modriansky M, Pichard-Garcia L, *et al*. Colchicine down-regulates cytochrome P450 2B6, 2C8, 2C9, and 3A4 in human hepatocytes by affecting their glucocorticoid receptor-mediated regulation. Mol pharmacol 2003;64:160–169.
25. Madan A, Graham RA, Carroll KM, *et al*. Effects of prototypical microsomal enzyme inducers on cytochrome P450 expression in cultured human hepatocytes. Drug Metab Dispos 2003;31:421–431.
26. Gerbal-Chaloin S, Pascussi JM, Pichard-Garcia L, *et al*. Induction of CYP2C genes in human hepatocytes in primary cultures. Drug Metab Dispos 2001;29:242–251.
27. Sahi J, Stern RH, Milad MA, *et al*. Effects of avasimibe on cytochrome P450 2C9 expression *in vitro* and *in vivo*. Drug Metab Dispos 2004;32:1370–1376.
28. Jeong HG, Yang KH. Expression of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-inducible cytochrome P4501A1 in human splenic lymphocyte cultures. Cancer Lett 1996;98:193–198.
29. Li W, Harper PA, Tang BK, *et al*. Regulation of cytochrome P450 enzymes by arylhydrocarbon receptor in human cells: CYP1A2 expression in the LS180 colon carcinoma cell line after treatment with 2,3,7,8-tetrachlorodibenzo-*p* dioxin or 3-methylcholanthrene. Biochem Pharmacol 1998;56:599–612.
30. Santostefano MJ, Ross DG, Savas U, *et al*. Differential time-course and dose-response relationships of TCDD-induced CYP1B1, CYP1A1, and CYP1A2 proteins in rats. Biochem Biophys Res Commu 1997;233:20–24.
31. Kedderis B, Mills JJ, Andersen ME, *et al*. A physiologically based pharmacokinetic model of 2,3,7,8-tetrabromodibenzo-*p*-dioxin (TBDD) in the rat: Tissue distribution and CYP1A induction. Toxicol Appl Pharmacol 1993;121:87–98.
32. Leung HW, Ku RH, paustenback DJ, *et al*. A physiologic-based pharmacokinetic model for 2,3,7,8-tetracholordibenzo-*p*-dioxin in C57BL/6J and DBA/2J mice. Toxicol Lett 1988;42:15–28.
33. Leung HW, Paustenback DJ, Murray FJ, *et al*. A phayiological pharmacokinetic model of tissue distribution and enzyme-inducing properties of 2,3,7,8-tetracholordibenzo-*p*-dioxin in the rat. Toxicol Appl Pharmacol 1990;103:399–410.
34. Krusekopf S, Kleeberg U, Hildebrandt AG, *et al*. Effects of benzimidazole derivatives on cytochrome P450 1A1 expression in a human cell line. Xenobiotica 1997;27:1–9.
35. Krusekopf S, Roots I, Hildebrandt AG, *et al*. Time-dependent transcriptional induction of CYP1A1, CYP1A2 and CYP1B1 mRNAs by $H^+/K^+$-ATPase inhibitors and other xenobiotics. Xenobiotica 2003;33:107–118.
36. McDonnell WM, Scheiman JM, Traber PG. Induction of cytochrome P450 1A genes (CYP1A) by omeprazole in human alimentary tract. Gastroenterology 1992;103: 1509–1516.
37. Rost KL, Brosick H, Heinemeyer G, *et al*. Specific and dose-dependent enzyme induction by omeprazole in human beings. Hepatology 1994;20:1204–1212.
38. Rost KL, Brosick H, Brockmoller J, *et al*. Increase of P450ia2 activity by omeprazole: evidence by the 13-C[N3-methyl]caffeine breath test in poor and extensive metabolizers of S-mephenytoin. Clin Pharmacol Ther 1992;52:170–180.
39. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther 2004;76:178–184.

40. Parkinson A, Thomas PE, Ryan DE, *et al*. The *in vivo* turnover of rat liver microsomal expoxide hydrolase and both the apoprotein and heme moieties of species cytochrome P-450 isozymes. Arch Biochem Biophys 1983;225:216–236.
41. Parkinson A, Thomas PE, Ryan DE, *et al*. Differential time course of induction of rat liver microsomal cytochrome P-450 isozymes and expoxide hydrolase by aroclor 1254. Arch Biochem Biophys 1983;225:203–215.
42. LeCluyse EL. Human hepatocyte culture systems for the *in vitro* evaluation of cytochrome P450 expression and regulation. Eur J Pharm Sci 2001;13:343–368.
43. Sahi J, Hamilton G, Sinze M, *et al*. Effects of troglitazone on cytochrome P450 enzymes in primary cultures of human and rat hepatocytes. Xenobiotica 2000;30:273–284.
44. Dougles JG, McLeod MJ. Pharmacokinetic factors in the morden drug treatment of tuberculosis. Clin Pharmacokint 1999;37:127–146.
45. Ohnhaus EE, Brockmeyer N, Dylewiez P, *et al*. The effect of antipyrin and rifampin on the metabolism of diazepam. Clin Pharmacol Ther 1987;42:148–156.
46. Herman RJ, Nakamura K, Wilkinson GR, *et al*. Induction of propranolol metabolism by rifampicin. Br J Clin Pharmacol 1983;16:565–569.
47. Orisakwe OE, Akunyili DN, Agbasi PU, *et al*. Some plasma and saliva pharmacokinetics parameters of rifampicin in the presence of pefloxacin. Am J Ther 2004;11:283–287.
48. Ndanusa BU, Mustapha A, Abdu-Aguye I. The effect of single dose of rifampicin on the pharmacokinetics of oral nifedipine. J Pharm Biomed Anal 1997;15:1571–1575.
49. Sayiner A, Ece T, Duman S, *et al*. Tuberculosis in renal transplant recipients. Transplantation 1999;68:1268–1271.
50. Sakhuja V, Jha V, Varma PP, *et al*. The high incidence of tuberculosis among renal transplant recipients in India. Transplantation 1996;61:211–215.
51. Modry DL, Stinson EB, Oyer PE. Acute rejection and massive cyclosporine requirements in heart transplant recipients treated with rifampin. Transplantation 1985;39:313–314.
52. Chenhsu RY, Loong CC, Chou MH, *et al*. Renal allograft dysfunction associated with rifampin-tacrolimus interaction. Ann Pharmacother 2000;34:27–31.
53. O'Reilly RA. Warfarin metabolism and drug-drug interactions. Adv Exp Med Biol 1987;214:205–212.
54. O'Reilly RA. Interaction of chronic daily warfarin therapy and rifampin. Ann Intern Med 1975;83:506–508.
55. Lee CR, Thrasher KA. Difficulties in anticoagulation management during coadministration of warfarin and rifampin. Pharmacotherapy 2001;21:1240–1246.
56. Self TH, Mann RB. Interaction of rifampin and warfarin. Chest 1975;67:490–491.
57. Twum-Barima Y, Carruthers SG. Quinidine-rifampin interaction. N Engl J Med 1981;304:1466–1469.
58. Hemeryck A, DeVriendt C, Belpaire FM. Effect of selective serotonin reuptake inhibitors on the oxidative metabolism of propafenone: *in vitro* studies using human liver microsomes. J Clin Psychopharmacol 2000;20:428–434.
59. Dilger K, Greiner B, Fromm MF, *et al*. Consequences of rifampicin treatment on propafenone disposition in extensive and poor metabolizers of CYP2D6. Pharmacogenetics 1999;9:551–559.
60. Yue QY, Sevesson JO, Alm C, *et al*. Codeine O-demethylation co-segregates with polymorphic debrisoquine hydroxylation. Br J Clin Pharmacol 1989;28:639–645.
61. Yue QY, Sevesson JO, Alm C, *et al*. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. Br J Clin Pharmacol 1991;31:635–642.
62. Armstrong SC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. Psychosomatics 2003;44:515–520.

63. Caraco Y, Sheller J, Wood AJ. Pharmacogenetic determinants of codeine induction by rifampin: the impact on codeine's respiratory, psychomotor and miotic effects. J Pharmacol Exp Ther 1997;281:330–336.
64. Coughtrie MWH, Ask B, Rane A, *et al*. The enantioselective glucuronidation of morphine in rats and humans. Evidence for the involvement of more than one UDP-glucuronosyltransferase isoenzyme. Biochem Pharmacol 1989;38:3273–3280.
65. Fromm MF, Eckhardt K, Li S, *et al*. Loss of analgesic effect of morphine due to coadministration of rifampin. Pain 1997;72:261–267.
66. Malaty LI, Kupper JJ. Drug interactions of HIV protease inhibitors. Drug Safety 1999;20:147–169.
67. Grub S, Bryson H, Goggin T, *et al*. The interaction of saquinavir (soft gelatin capsule) with ketoconazole, erythromycin and rifampicin: comparison of the effect in healthy volunteers and in HIV-infected patients. Eur J Clin Pharmacol 2001;57:115–121.
68. Nelfinavir mesylate (Viracept®) prescribing information. La Jolla (CA): Agouron Pharmaceuticals; 2001.
69. Norvir® package insert, Illinois: Abbott Laboratories; 1997.
70. Efavirenz (Sustiva®) package insert. New Jersey: Bristol-Myers Squibb Company; 2002.
71. Fiske WD, Mayers D, Wagner K. Pharmacokinetics of DMP 266 and indinavir multiple oral doses in HIV-1 infected individuals. In: 4th Conference on Retroviruses and Opportunistic Infections; Washington (DC): 1996. Jan 28–Feb 1. Abstract No. 568.
72. Ju C, Uetrecht J. Mechanism of idiosyncratic drug reaction: reactive metabolite formation, protein binding and the regulation of immune system. Curr Drug Metab 2002;3:367–377.
73. Urtrecht J. Screening for the potential of a drug candidate to cause idiosyncratic drug reaction. DDT 2003;18:832–837.
74. Okey AB, Franc MA, Moffat ID, *et al*. Toxicological implications of polymorphisms in receptors for xenobiotic chemicals: the case of the aryl hydrocarbon receptor. Toxicol Appl Pharmacol 2005;207:43–51.
75. Nebert DW, Dalton TP, Okey AB, *et al*. Role of aryl hydrocarbon receptor-mediated induction of CYP1 enzymes in environmental toxicity and cancer. J Biol Chem 2004; 279:23847–23850.
76. Okey AB. Enzyme induction in the cytochrome P-450 system. Pharmacol Ther 1990; 45:241–298.
77. Conney AH. Enzyme induction and dietary chemicals as approaches to cancer chemoprevention: the seventh DeWitt S. Goodman lecture Cancer Res 2003;63:7005–7031.
78. Tonnesen P, Pisinger C, Hvidberg S, *et al*. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res 2005;7:139–148.
79. Cantani A, Micera M. Epidemiology of passive smoke: a prospective study in 589 children. Eur Rev Med Pharmacol Sci 2005;9:23–30.
80. Brooks DR, Austin JH, Heelan RT, *et al*. Influence of type of cigarette on peripheral versus central lung cancer. Cancer Epidemiol Biomarkers Prev 2005;14:576–581.
81. Witschi H, Espiritu I, Peake JL, *et al*. The carcinogenicity of environmental tobacco smoke. Carcinogenesis 1997;18:575–586.
82. Lieber CS. Cytochrome P-4502E1: Its physiological and pathological role. Physiol Rev 1997;77:517–544.
83. Cederbaum AI. Microsomal generation of reactive oxygen species and their role in alcohol hepatotoxicity. Alcohol Alcsm 1991;suppl 1:291–296.
84. Ekstrom G, Ingelman-Sundberg M. Rat liver microsomal NADPH-supported oxidase activity and lipid peroxidation dependent on ethanol-inducible cytochrome P450 (P-450IIEI). Biochem Pharmacol 1989;38:1313–1319.
85. Rashba-Step J, Turro NJ, Cederbaum AI. Increased NADPH-dependent production of superoxide and hydroxyl radical by microsomes after chronic ethanol treatment. Arch Biochem Biophys 1993;300:401–408.

86. Dai Y, Rashba-Step J, Cederbaum AI. Stable expression of human cytochrome P4502E1 in HepG2 cells: characterization of catalytic activities and production of reactive oxygen intermediates. Biochemistry 1993;32:6928–6937.
87. Morimoto M, Hagbjork AL, Yvonne Wan YJ, *et al*. Modulation of experimental alcohol-induced liver disease by cytochrome P450 2E1 inhibitors. Hepatology 1995;21:1610–1617.
88. Kukielka E, Cederbaum AI. DNA strand cleavage as a sensitive assay for the production of hydroxyl radicals by microsomes: role of cytochrome P4502E1 in the increased activity after ethanol treatment. Biochem J 1994;302:773–779.
89. Slattery JT, Nelson SD, Thummel KE. The complex interaction between ethanol and acetaminophen. Clin Pharmacol Ther 1996;60:241–246.
90. Raucy JL, Lasker JM, Lieber CS, *et al*. Acetaminophen activation by human liver microsomes P450Iie1 and P450ia2. Arch Biochem Biophys 1989;271:270–283.
91. Zand R, Nelson SD, Slattery JT, *et al*. Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. Clin Pharmacol Ther 1993;54:142–149.
92. Thummel KE, Lee CA, Kunze KL, *et al*. Oxidation of acetaminophen to N-acetyl-p-benzoquinone imine by human CYP3A4. Biochem Pharmacol 1993;45:1563–1569.
93. Lee SST, Buters JTM, Pineaus T, *et al*. Role of CYP2E1 in hepatotoxicity of acetaminophen. J Biol Chem 1996;271:12063–12067.
94. Zaher H, Buters JTM, Ward JM, *et al*. Protection against acetaminophen toxicity in CYP1A2 and CYP2E1 double-null mice. Toxicol Appl Pharmacol 1998;152:193–199.
95. Tonge RP, Kelly EJ, Bruschi SA, *et al*. Role of CYP1A2 in the hepatoxicity of acetaminophen: investigations using CYP1a2 null mice. Toxicol Appl Pharmacol 1998;153:102–108.
96. Sarich T, Kalhorn T, Magee S, *et al*. The effect of omeprazole pretreatment on acetaminophen metabolism in rapid and slow metabolizers of S-mephenytoin. Clin Pharmacol Ther 1997;62:21–28.
97. Guo GL, Moffit JS, Nicol CJ, *et al*. Enhanced acetaminophen toxicity by activation of the pregnane X receptor. Toxicol Sci 2004;82:374–380.
98. Manyike PT, Kharasch ED, Kalhorn TF, *et al*. Contribution of CYP2E1 and CY3A to acetaminophen reactive metabolite formation. Clin Pahramcol Ther 2000;67:275–282.
99. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: Clinical implications. Clin Pharmacokinet 2003;42:59–98.
100. Lin JH. Drug-drug interaction mediated by inhibition and induction of P-glycoprotein. Adv Drug Delivery Rev 2003;55:53–81.
101. Benet LZ, Cummins CL, Wu CY. Transporter-enzyme interactions: Implications for predicting drug-drug interactions from *in vitro* data. Curr Drug Metab 2003;4:393–398.
102. Benet LZ, Cummins CL, Wu CY. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. Int J Pharmaceutics 2004;277:3–9.