Absorption, Distribution, Metabolism and Elimination: Part II

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Aspirin Metabolism

Organs Involved in Drug Biotransformation

- Liver
- Gastrointestinal mucosa
- Lung
- Skin
- Placenta
Schematic model of the cytochrome P450-cytochrome P450 reductase complex in liver microsomal membranes. The scattered (blue) glycogen around the complex are in a rigid state below the transition temperature of 31°C, whereas the bulk of the fluid in which the complex is embedded is in a conecopy flexible condition (courtesy of Prof. A. Stein).

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Figure 1-1. The proportion of drugs metabolized by the major cytochrome P450 enzymes.

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Figure 1-3. Major components of the hepatic microsomal drug-metabolizing enzyme system.
1. Oxidation
   a. Aromatic hydroxylation

   ![Aromatic hydroxylation diagram]

   \[ \text{Phenytoin} \rightarrow \text{Phenytoin hydroxylation product} \]

b. Aliphatic hydroxylation

   ![Aliphatic hydroxylation diagram]

   \[ \text{Meprobamate} \rightarrow \text{Meprobamate hydroxylation product} \]

d. Oxidative O-dealkylation

   ![Oxidative O-dealkylation diagram]

   \[ \text{Phenacetin} \rightarrow \text{Acetaminophen} \]
4. S-oxidation

\[
\begin{align*}
\text{Chlorpromazine} & \\
\end{align*}
\]

4. Conjugation

a. Glycine

\[
\begin{align*}
\text{Salicylic acid} & \\
\end{align*}
\]

b. Glucuronic acid

\[
\begin{align*}
\text{Chloramphenicol} & \\
\end{align*}
\]
d. Acetylation

Examples of Characteristic Inducers of the Major P450 Gene Families

CYP 1A2: Tobacco
CYP 2C19: Prednisone
CYP 2C9: Rifampin
CYP 2D6: Dexamethasone?
CYP 2E1: Ethanol
CYP 3A4, 5, 7: Barbiturates
The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron

Background: Ondansetron is an ataractic agent marketed for the prevention of chemotherapy-induced nausea and vomiting after chemotherapy. This study examined the pharmacokinetics of oral and intravenous administration of ondansetron with and without rifampin (rifampicin; Rifadin, Medac). Rifampin is a potent inducer of CYP3A4 and could affect CYP3A4 metabolism. Therefore, the primary objective of this study was to evaluate the effect of rifampin on the pharmacokinetics of ondansetron administered orally and intravenously.

Methods: The study was a randomized, open-label study with two treatment groups: 10 healthy volunteers were administered 8 mg oral ondansetron plus placebo or placebo plus 600 mg rifampin on day 1, and 10 healthy volunteers were administered 8 mg intravenous ondansetron plus placebo or placebo plus 600 mg rifampin on day 1. On day 8, the oral dose was repeated, and on day 2, they were administered 8 mg intravenous ondansetron plus placebo or placebo plus 600 mg rifampin on day 2.

Results: On day 1, the mean oral area under the curve (AUC) of placebo was 38.8 ± 19.6 mg·h/L, and on day 2, the mean oral AUC of placebo was 39.1 ± 21.3 mg·h/L. On day 1, the mean intravenous AUC of placebo was 22.8 ± 11.5 mg·h/L, and on day 2, the mean intravenous AUC of placebo was 22.9 ± 11.0 mg·h/L. No significant differences were observed in the AUCs of either oral or intravenous ondansetron for either group.

Conclusion: The results of this study suggest that rifampin does not significantly affect the pharmacokinetics of oral or intravenous ondansetron. However, rifampin may lead to an increased variability in the pharmacokinetics of ondansetron, and further studies are needed to confirm these findings.

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Clinical Pharmacology & Therapeutics

Figure 1. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after oral administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. Open circles, After placebo; solid circles, after rifampin.

Figure 2. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after intravenous administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. Open circles, After placebo; solid circles, after rifampin.
Examples of Inhibitors of the Major P450 Gene Families

CYP 1A2: Cimetidine
CYP 2C19: Ketoconazole
CYP 2C9: Isoniazid
CYP 2D6: Cimetidine
CYP 2E1: Water Cress
CYP 3A4, 5, 7: Cimetidine, grapefruit juice

PHARMACOKINETICS AND DRUG DISPOSITION

Grapefruit juice and cimetidine inhibit stereoselective metabolism of nitrendipine in humans

The effects of grapefruit juice (150 ml at -15, -10, -5, 0, 5, and 10 hours) and cimetidine (200 mg at the same times) on the stereoselective pharmacokinetics and effects of 20 mg oral racemic nitrendipine were investigated in a placebo-controlled crossover study in nine healthy men. In all subjects the AUC of racemic nitrendipine was increased by grapefruit juice (mean increase 100%, 95% confidence interval 66% to 186%) and cimetidine treatment (+14%, 95% confidence interval 77% to 266%). Comparable results were obtained for the peak plasma drug concentration and for both parameters of (R)- and (S)-nitrendipine. There were highly significant differences in the area under the concentration-time curve...
Grapefruit juice substantially increases plasma concentrations of buspirone

Background: Buspirone has a low oral bioavailability because of extensive first-pass metabolism. The effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of orally administered buspirone is not known.

Methods: In a randomized, 1-phase crossover study, 30 healthy volunteers each either 250 ml double-strength grapefruit juice or water were given 1 mg buspirone with either 250 ml grapefruit juice or water, and an additional 250 ml was ingested 1 hour and 7 hours after buspirone administration. Venous blood samples were collected up to 12 hours after ingestion and the effect of buspirone was measured with 5-ht1a receptor assays up to 3 hours after ingestion. Results: Grapefruit juice increased the mean peak plasma concentration of buspirone 4.5 fold (range, 2-fold to 6.8-fold, p < 0.001) and the area under the plasma buspirone concentration-time curves 9.3 fold (range, 3.6-fold to 26.4 fold, p < 0.001). The time to the peak concentration (tmax) of buspirone increased from 0.1 to 3 hours (p < 0.01), and the elimination half-life (t1/2) was slightly decreased (p < 0.05) by grapefruit juice. A significant increase in the pharmacodynamic effects of buspirone by grapefruit juice was seen only in subjective overall drug effect (p = 0.03).

Conclusion: Grapefruit juice increases plasma buspirone concentrations. This probably explains much of the literature on adverse events reported in the literature. Further studies are needed to confirm these findings and elucidate the mechanisms involved. A health care warning on grapefruit juice and buspirone should be developed. (Clin Pharmacol Ther 1998;63:65-8.)

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Erythromycin (an antibiotic) and Verapamil (a calcium channel blocker) are also important inhibitors of P-450.
Inhibition of chloroxazone metabolism, a clinical probe for CYP2E1, by a single ingestion of watercress

To investigate the effect of watercress on the metabolism of chloroxazone, as a probe for CYP2E1, the oral pharmacokinetics of chloroxazone was studied in 10 healthy volunteers before and after a single ingestion of a watercress homogenate (50 g). A third chloroxazone pharmacokinetics study was performed after a 3-week treatment with licorice (200 mg/day), a well-known CYP2E1 inducer. Inhibition of watercress or licorice did not affect the oral absorption of chloroxazone. The area under the chloroxazone plasma concentration-time curve was significantly increased by 58% (p < 0.05) after watercress ingestion and by 15% (p < 0.01) with licorice treatment. Similarly, chloroxazone elimination half-life was prolonged after watercress (15%, p < 0.05) and licorice (14%, p < 0.01) administration. These results show that a single ingestion of watercress inhibits the hydroxylation of chloroxazone, as in vivo probe for CYP2E1. (Clin Pharmacol Ther 100:340-346)

Isabelle Lechevallier, Jean-Pierre Desager, and Yves Horsmans.

Debrisoquine

4-Hydroxydebrisoquine

Fig. 7.1. Chemical structure of debrisoquine and its major metabolite, 4-hydroxydebrisoquine. (From Maggoux et al. 1977.)
Pharmacokinetics of metoprolol enantiomers in Chinese subjects of major CT12I36 genotypes

Objective: CT12I36 polymorphism might be a determinant of pharmacokinetics in Chinese subjects. The objectives of the current study were to evaluate the difference in pharmacokinetics between the major genotypes and whether differences could be found among subjects with XIN syndrome genotypes.

Methods: A selective polymorphism study was conducted in Chinese subjects with CT12I36 allele T or CT12I36 allele C. The subjects were divided into two groups: Group A (CT12I36 allele T) and Group B (CT12I36 allele C). The pharmacokinetic parameters were evaluated by comparing the plasma concentration-time profiles between the two groups.

Results: A significant difference was observed in the pharmacokinetic parameters between the two groups. The area under the plasma concentration curve (AUC) for Group A was higher than that for Group B. The half-life (t1/2) was also longer in Group A compared to Group B.

Conclusion: The results suggest that the CT12I36 polymorphism may have an impact on the pharmacokinetics of metoprolol in Chinese subjects. Future studies are needed to further investigate the role of this polymorphism in pharmacokinetics.

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Figure 2. Plasma concentration of S-metoprolol (left) and R-metoprolol (right) after oral administration of a single dose of metoprolol (100 mg) in Chinese subjects of 3 different CT12I36 genotypes. Legend: Group A: Carriers of metoprolol C12I36 allele T; Group B: Heterozygous C12I36 allele T/C; Group C: Heterozygous C12I36 allele C/C. The bars indicate SEM.
Figure 1-4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.