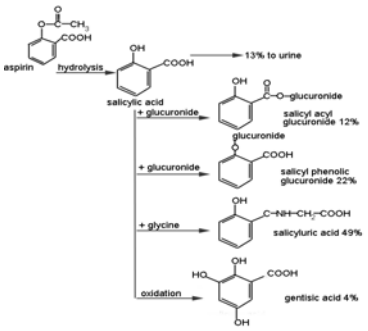
Absorption, Distribution, Metabolism and Elimination: Part II

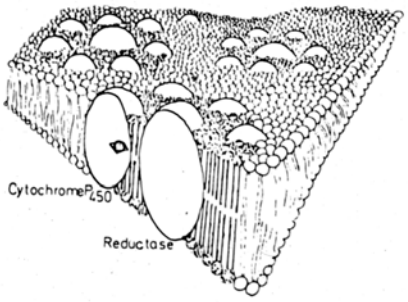
Joseph Graziano, Ph.D.

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 shaded lipids segregated around the complex are in a rigid state below the transition temperature of 32°, whereas the bulk of the lipid in which the complex is embedded is in a completely fluid condition. (Courtesy of Prof. A. Stier).

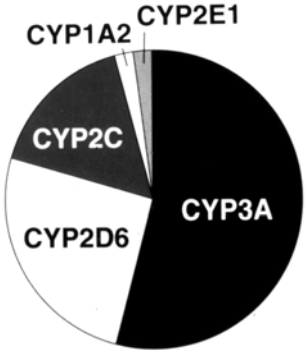
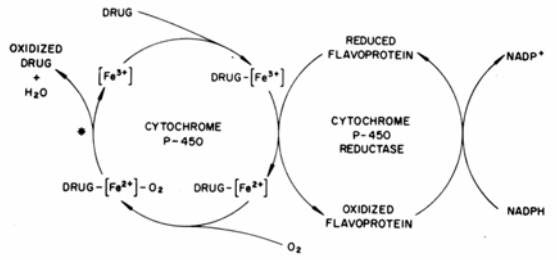


Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.

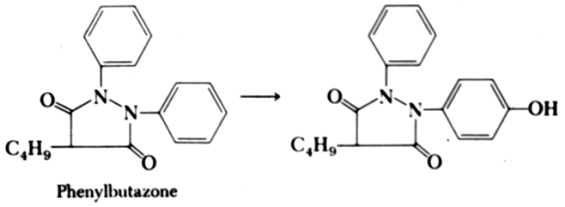


* Denotes contribution of a second electron and two hydrogen ions from NADH–flavoprotein–cytochrome b_5 or from NADPH–flavoprotein.

Figure 1–3. *Major components of the hepatic microsomal drug-metabolizing enzyme system.*

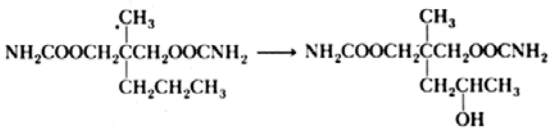
1.Oxidation

a. Aromatic hydroxylation



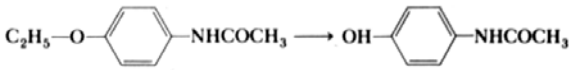
Phenylbutazone

b. Aliphatic hydroxylation



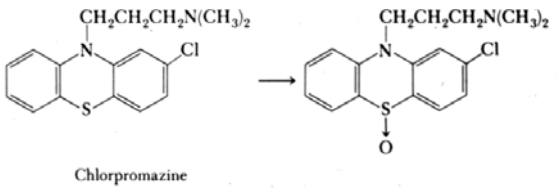
Meprobamate

d. Oxidative O-dealkylation



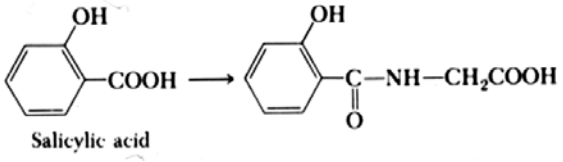
Phenacetin Acetaminophen

e. S-oxidation



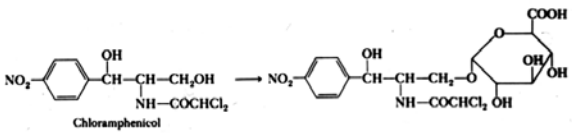
Chlorpromazine

4. Conjugation
a. Glycine



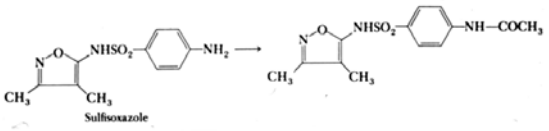
Salicylic acid

b. Glucuronic acid



Chloramphenicol

d. Acetylation



Sulfisoxazole

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

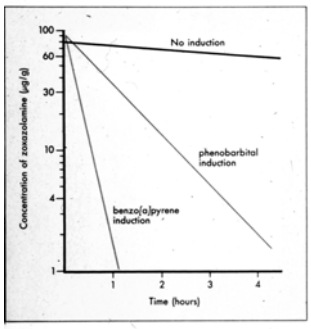


FIGURE 5-10 Example of enzyme induction. Zoxazolamine administered by intraperitoneal injection to rats. For induction studies phenobarbital or 3,4l-benzo[a]pyrene were injected twice daily for 4 days before injection of the zoxazolamine. Drug concentration is expressed as μg drug / gram of tissue.

The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron

Background: Ondansetron is an antiemetic agent metabolized by cytochrome P450 (CYP) enzymes. Rifampin (INN, rifampicin) is a potent inducer of CYP3A4 and some other CYP enzymes. We examined the possible effect of rifampin on the pharmacokinetics of orally and intravenously administered ondansetron.

Methods: In a randomized crossover study with 4 phases and a washout of 4 weeks, 10 healthy volunteers took either 600 mg rifampin (in 2 phases) or placebo (in 2 phases) once a day for 5 days. On day 6, 8 mg ondansetron was administered either orally (after rifampin and placebo) or intravenously (after rifampin and placebo). Ondansetron concentrations in plasma were measured up to 12 hours.

Results: The mean total area under the plasma concentration–time curve [AUC(0→∞)] of orally administered ondansetron after rifampin pretreatment was reduced by 65% compared with placebo ($P < .001$). Rifampin decreased the peak plasma concentration of oral ondansetron by about 50% (from 27.2 ± 3.0 to 13.8 ± 1.5 ng/mL [mean ± SEM]; $P < .001$]) and the elimination half-life ($t_{1/2}$) by 38% ($P < .01$). The bioavailability of oral ondansetron was reduced from 60% to 40% ($P < .01$) by rifampin. The clearance of intravenous ondansetron was increased 83% (from 440 ± 38.4 to 805 ± 44.6 mL/min [$P < .001$]) by rifampin. Rifampin reduced the $t_{1/2}$ of intravenously administered ondansetron by 46% ($P < .001$) and the AUC(0→∞) by 48% ($P < .001$).

Conclusions: Rifampin considerably decreases the plasma concentrations of ondansetron after both oral and intravenous administration. The interaction is most likely the result of induction of the CYP3A4-mediated metabolism of ondansetron. Concomitant use of rifampin or other potent inducers of CYP3A4 with ondansetron may result in a reduced antiemetic effect, particularly after oral administration of ondansetron. (Clin Pharmacol Ther 1999;65:377-81.)

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APRIL 1999

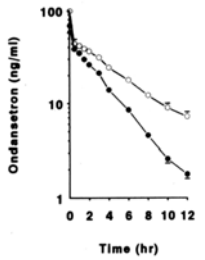

Figure 2. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after intravenous administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. *Open circles*, After placebo; *solid circles*, after rifampin.

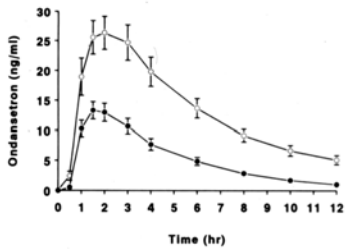

Figure 1. Plasma concentrations (mean ± SEM) of ondansetron in 10 subjects after oral administration of 8 mg ondansetron following pretreatment with 600 mg rifampin or placebo once daily for 5 days. *Open circles*, After placebo; *solid circles*, after rifampin.

Table 14. Cimetidine inhibits the hepatic elimination of:

Acenocoumarol	Desmethyldiazepam	Lidocaine	Quinidine
Alcohol	Diazepam	Metoprolol	Quinine
Alprazolam	Doxepine	Metronidazole	Salicylic acid
Antipyrine	Ethmozine	Nifedipine	Theobromine
Bromazepam	Femoxetine	Nitrazepam	Theophylline
Caffeine	5-Fluorouracil	Pefloxacine	Triamterene
Carbamazepam	Glibenclamide	Phenandione	Triazolam
Chlordiazepoxide	Gliclazide	Phenytoin	Trimazosine
Chlormethiazole	Imipramine	Procainamide	Valproic acid
Clobazam	Labetalol	Propranolol	Verapamil
			Warfarin

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, −¼, +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 106%; 95% confidence interval 64% to 158%) and cimetidine treatment (+154%; 95% confidence interval 77% to 265%). Comparable results were obtained for the peak plasma drug concentration and for both parameters of (S)- and (R)-nitrendipine. There were highly significant differences in the area under the concentration-time curve

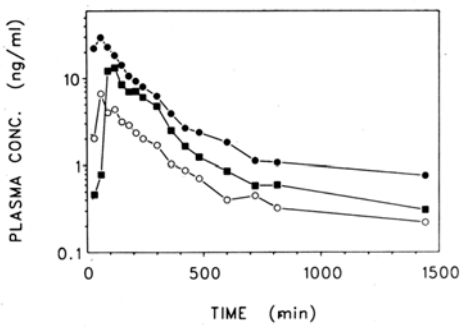

Fig. 1. Typical plasma concentration-time profiles of racemic nitrendipine in an individual subject with concomitant placebo (○), grapefruit juice (■), and cimetidine treatment (●).

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, 2-phase crossover study, 10 healthy volunteers took either 200 mL double-strength grapefruit juice or water 3 times a day for 2 days. On day 3, each subject ingested 10 mg buspirone with either 200 mL grapefruit juice or water, and an additional 200 mL was ingested ½ hour and 1½ hours after buspirone administration. Timed blood samples were collected up to 12 hours after ingestion, and the effects of buspirone were measured with 6 psychomotor tests up to 8 hours after ingestion.

Results: Grapefruit juice increased the mean peak plasma concentration of buspirone 4.3-fold (range, 2-fold to 15.6-fold; $P < .01$) and the mean area under the plasma buspirone concentration–time curve 9.2-fold (range, 3-fold to 20.4-fold; $P < .01$). The time of the peak concentration (t_{max}) of buspirone increased from 0.75 to 3 hours ($P < .01$), and the elimination half-life ($t_{1/2}$) was slightly increased ($P < .01$) by grapefruit juice. A significant increase in the pharmacodynamic effects of buspirone by grapefruit juice was seen only in subjective overall drug effect ($P < .01$).

Conclusions: Grapefruit juice considerably increased plasma buspirone concentrations. The probable mechanism of this interaction is delayed gastric emptying and inhibition of the cytochrome P450 3A4–mediated first-pass metabolism of buspirone caused by grapefruit juice. Concomitant use of buspirone and at least large amounts of grapefruit juice should be avoided. (Clin Pharmacol Ther 1998;64:655-60.)

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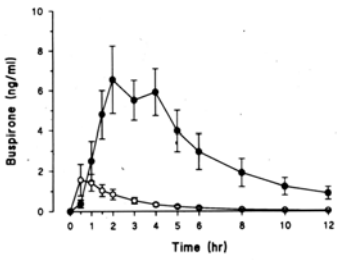

Figure 1. Plasma concentrations (mean value ± SEM) of buspirone among 10 healthy volunteers after a single oral dose of 10 mg buspirone, after ingestion of 200 mL double-strength grapefruit juice *(solid circles)* or water *(open circles)* 3 times a day for 2 days, and on day 3 with buspirone administration and ½ hour and 1½ hours later.

PHARMACOKINETICS AND DRUG DISPOSITION

Grapefruit juice–simvastatin interaction: Effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors

Background. Simvastatin is a cholesterol-lowering agent that is metabolized through CYP3A4. We studied the effect of grapefruit juice on the pharmacokinetics of orally administered simvastatin.

Methods. In a randomized, 2 phase crossover study, 10 healthy volunteers took either 200 mL double-strength grapefruit juice or water 3 times a day for 2 days. On day 3, each subject ingested 60 mg simvastatin with either 200 mL grapefruit juice or water, and an additional 200 mL was ingested ½ and 1½ hours after simvastatin administration. Serum concentrations of simvastatin and simvastatin acid were measured by liquid chromatography–tandem mass spectrometry (LC-MS-MS) and those of active (naive) and total (after hydrolysis) 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors by a radioenzyme inhibition assay.

Results. Grapefruit juice increased the mean peak serum concentration (C_{max}) of unchanged simvastatin about 9-fold (range, 5.1-fold to 31.4-fold, $P < .01$) and the mean area under the serum simvastatin concentration–time curve [AUC(0→∞)] 16-fold (range, 9.0-fold to 37.7-fold; $P < .05$). The mean C_{max} and AUC(0→∞) of simvastatin acid were both increased about 7-fold ($P < .01$). Grapefruit juice increased the mean AUC(0→∞) of active and total HMG-CoA reductase inhibitors 2.4-fold ($P < .01$) and 3.6-fold ($P < .01$), respectively. The time of the peak concentration of active and total HMG-CoA reductase inhibitors was increased by grapefruit juice ($P < .05$).

Conclusion. Grapefruit juice greatly increased serum concentrations of simvastatin and simvastatin acid and, to a lesser extent, those of active and total HMG-CoA reductase inhibitors. The probable mechanism of this interaction was inhibition of CYP3A4-mediated first-pass metabolism of simvastatin by grapefruit juice in the small intestine. Concomitant use of grapefruit juice and simvastatin, at least in large amounts, should be avoided, or the dose of simvastatin should be greatly reduced. (Clin Pharmacol Ther 1998;64:477-83.)

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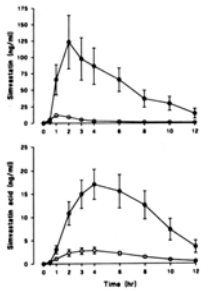


Figure 1. Mean ± SEM serum concentrations of simvastatin (**upper panel**) and simvastatin acid (**lower panel**) in 10 healthy volunteers after a single oral dose of 60 mg simvastatin, after ingestion of 200 mL double-strength grapefruit juice *(solid circles)* or water *(open circles)* 3 times a day for 2 days and on day 3 with simvastatin and ½ hour and 1½ hours later.

Erythromycin (an antibiotic) and Verapamil (a calcium channel blocker) are also important inhibitors of P-450

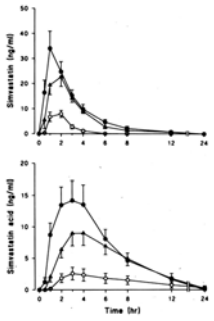
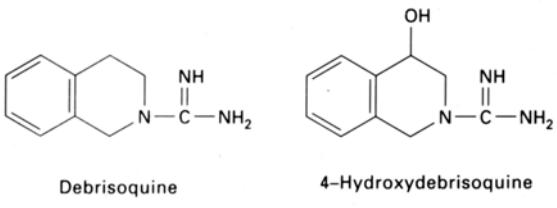


Fig. 1. Serum concentrations (mean ± SE) of simvastatin (**top panel**) and simvastatin acid (**bottom panel**) for 12 subjects after administration of 40 mg oral simvastatin and after pretreatment with 1.5 gm/day erythromycin (*solid circles*), 240 mg/day verapamil (*solid triangles*), or placebo (*open circles*) orally for 2 days.

Inhibition of chlorzoxazone metabolism, a clinical probe for CYP2E1, by a single ingestion of watercress

To investigate the effect of watercress on the metabolism of chlorzoxazone, an in vivo probe for CYP2E1, the oral pharmacokinetics of chlorzoxazone was studied in 10 healthy volunteers before and after a single ingestion of a watercress homogenate (50 gm). A third chlorzoxazone pharmacokinetic study was performed after a 1-week treatment with isoniazid (300 mg/day), a well-known CYP2E1 inhibitor. Ingestion of watercress or isoniazid did not affect the oral absorption of chlorzoxazone. The area under the chlorzoxazone plasma concentration–time curve was significantly increased by 56% ($p < 0.05$) after watercress ingestion and by 135% ($p < 0.001$) with isoniazid treatment. Similarly, chlorzoxazone elimination half-life was prolonged after watercress (53%; $p < 0.05$) and isoniazid (104%; $p < 0.01$) administration. These results show that a single ingestion of watercress inhibits the hydroxylation of chlorzoxazone, an in vivo probe for CYP2E1. (Clin Pharmacol Ther 1998;64:144-9.)

Isabelle Leclercq, Jean-Pierre Desager, and Yves Horsmans *Brussels, Belgium*



Debrisoquine — 4–Hydroxydebrisoquine

Fig. 7.1. Chemical structure of debrisoquine and its major metabolite, 4-hydroxydebrisoquine. (From Mahgoub *et al.* 1977.)

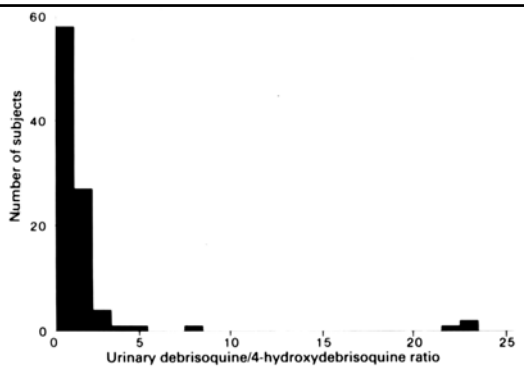


Fig. 7.2. Frequency distribution of the ratio, urinary debrisoquine/4-hydroxydebrisoquine, in 94 human volunteers. (From Mahgoub *et al.* 1977.)

Pharmacokinetics of metoprolol enantiomers in Chinese subjects of major *CYP2D6* genotypes

Objective: CYP2D6 mediates both α-hydroxylation and *O*-demethylation of metoprolol. In Chinese subjects, *CYP2D6*1* (the wild-type) alleles are relatively uncommon. Subjects with P34S (C_{188}→T_{188}) and S486T (C_{4268}→G_{4268}) mutations (*CYP2D6J* or *CYP2D6*10A*) are more frequently seen. Recently, the *CYP2D6*2* (*CYP2D6L*) genotype that results in R296C (C_{2938}→T_{2938}) and S486T mutations was also found important. In this study, metoprolol pharmacokinetics was investigated in subjects of these 3 major genotypes.

Methods: Allele-specific polymerase chain reaction was used to differentiate *CYP2D6*1* and *CYP2D6*2* alleles from the common *CYP2D6*10A* allele in Chinese. Subjects with both *CYP2D6*1* and *CYP2D6*2* have homozygous C_{188} in the exon 1, whereas subjects with *CYP2D6*10A* have T_{188}. Metoprolol pharmacokinetics was compared in 16 C_{188} subjects (6 homozygous *CYP2D6*1* subjects and 10 heterozygous *CYP2D6*1/CYP2D6*2* subjects), 12 heterozygous C/T_{188} subjects, and 12 homozygous T_{188} subjects.

Results: No significant difference in plasma concentration profile or urinary α-hydroxymetoprolol excretion could be found among subjects with R296C polymorphism *(CYP2D6*1/CYP2D6*2)*. Therefore data from subjects with *CYP2D6*1* and *CYP2D6*2* were pooled to compare with data from subjects with *CYP2D6*10A*. The area under plasma concentration curves (AUC) of *S*-metoprolol was 1411 ± 116 (mean ± SEM, *n* = 16), 1899 ± 120 (*n* = 12), and 3588 ± 435 (*n* = 12) nmol · hr/L for homozygous C_{188}, heterozygous C/T_{188}, and homozygous T_{188} subjects, respectively. The urinary recovery of all 4 α-hydroxymetoprolol diastereomers was significantly lower in T_{188} subjects than in C_{188} subjects.

Conclusion: The P34S polymorphism but not the R296C polymorphism resulted in higher metoprolol plasma concentrations and lower urinary metoprolol metabolite levels in Chinese subjects. This finding suggests that a lower dose of metoprolol may be used in subjects with T_{188} mutation (*CYP2D6*10A* allele). (Clin Pharmacol Ther 1999;65:402-7.)

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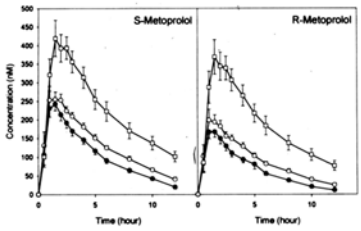

Figure 2. Plasma concentration of *S*-metoprolol **(left)** and *R*-metoprolol **(right)** after oral administration of a single dose of the racemate (100 mg) in Chinese subjects of 3 different C/T_{188} genotypes. *Solid circles*, Homozygous C_{188} (n = 16); *open circles*, heterozygous C/T_{188} (n = 12); *squares*, homozygous T_{188} (n = 12). The *bars* indicate SEM.

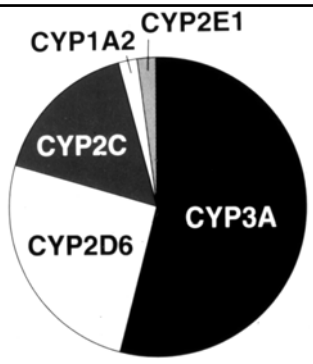

Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.