

3. P450 Drug Metabolism DDIs: Induction (2012)

General Introduction and Definition of a DDI:

A drug-drug interaction (DDI) occurs when two drugs, each of which is safe and efficacious alone at their respective doses, produce either a toxic or subtherapeutic effect when given in combination.

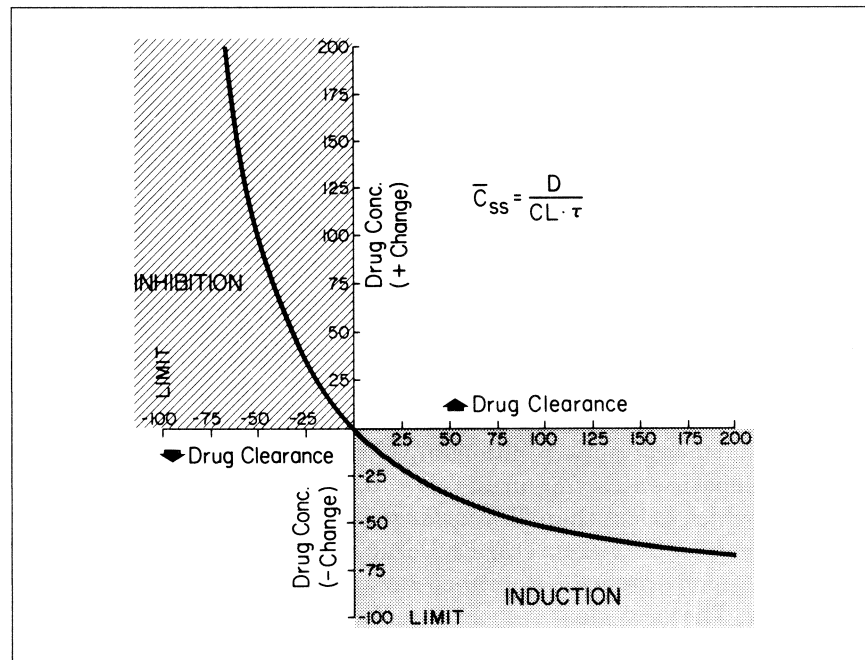


FIGURE 6-2. The relationship between the percent change in drug clearance to the percent change in the steady-state average drug concentration. Drug clearance is oral when the drug is administered orally and systemic when administered parenterally. The maximum decrease in drug clearance is 100% and the maximum decrease in the steady-state drug concentration is 100%.

Metabolism-based DDIs: A substantial fraction of drug-drug interactions occur as the result of drug induced changes in drug metabolizing capacity (metabolic clearance).

Metabolic drug-drug interactions, when anticipated, can often be managed or avoided by:

1. Selecting a different non-interacting pair
2. Dose changes of the object drug adjustments at the initiation and termination of polytherapy.

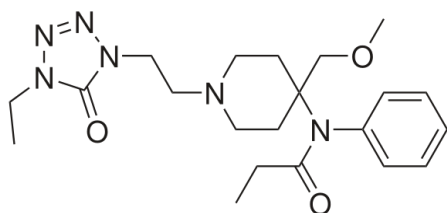
For convenience we will refer to the two drugs as the object drug the interactant drug.

Object Drug: The drug whose metabolism has been altered by the Interactant Drug.

Interactant Drug: The drug that is causing a change in the activity or amount of the drug metabolising enzymes that control the metabolic clearance of the object drug.

Effect of an Interactant Drug on Active P450 Levels	Condition	Effect of Interactant Drug on Object Drug Clearance (Cl)	Effect of Interactant Drug on Object Drug Half-life ($t_{1/2}$)
↓	Enzyme Inhibition	↓	↑
↑	Enzyme Induction	↑	↓

Let's look at an example where we see both effects on a single object drug:



Alfentanil (synthetic opioid for parenteral use) metabolic clearance via N-dealkylation to nor-alfentanil by CYP3A4. Other drugs in the class are fentanyl and remifentanyl (also CYP3A substrates).

Rifampicin is an antibacterial used in the treatment of tuberculosis. It is a general and potent inducer of P450 enzymes including CYP3A4, CYP2C9 and CYP2C19.

Troleandomycin (TAO) is an erythromycin analog and a potent selective inhibitor of CYP3A4 in vivo. Erythromycin and clarithromycin (another erythromycin analog) are also selective inhibitors of CYP3A4 and produce significant interactions but are not as potent as TAO at normal doses.

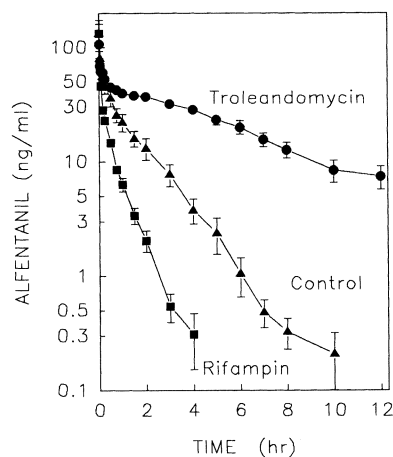
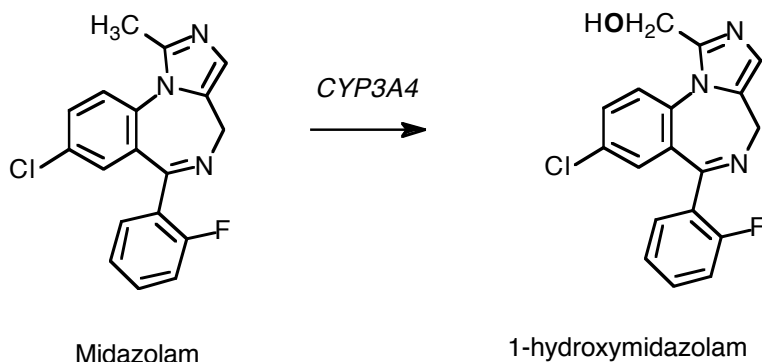


FIG. 22-12. Effect of CYP3A4 activity on alfentanil disposition. Shown are plasma concentrations in subjects receiving nothing (diamonds), rifampin for 5 days (squares), or troleandomycin 3 hours (circles) before a single i.v. alfentanil bolus. Clearance (mean \pm SD) in the three groups was 5.3 ± 2.3 mL/kg/min, 14.6 ± 3.8 mL/kg/min, and 1.1 ± 0.5 mL/kg/min. Reproduced from Kharasch ED, Russell M, Mautz D, et al. The role of cytochrome P450 3A4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997;87:36–50, with permission.

PK parameter	Control	Rifampin	Troleandomycin
Cl ($\text{mL kg}^{-1} \text{min}^{-1}$)	5.3	14	1.1
Vd (L/kg)	0.43	0.56	0.52
T _{1/2} (min)	58	35	630

Let's look at another example using a different object drug midazolam i.v. and the same two interactant drugs. CYP3A4 controls about 90% of midazolam clearance.

(a)



<u>Midazolam</u>	<u>Coadministered Drug</u>		
	<u>Rifampin</u>	<u>None</u>	<u>Troleandomycin</u>
Half-life (hr)	1.5 (↓)	3	15 (↑)
Clearance (ml kg ⁻¹ min ⁻¹)	8.7 (↑)	3.3	0.8 (↓)

So we see exactly the same pattern of effect on half-life and clearance. Note that the magnitude of the effect of induction is less than the magnitude of effect for Troleandomycin. Erythromycin is also a clinically significant inhibitor of CYP3A4.

Why is it important that we can draw these patterns and correlations from clinical studies?....Because it reduces the number of studies that need to be done for any given object drug where we are worried about an interaction.

Corollary: If a group of object drugs are metabolised significantly by a given enzyme then the effect of a given interactant drug on clearance should be seen for all of those object drugs.

2) Induction of P450 Enzymes:

- a) Note: Induction of P450 enzyme levels normally takes days to reach full effect. Similarly de-induction due to removal of an inducing agent also takes days to reach completion. If the levels of the P450 enzyme(s) that are responsible for metabolizing an object drug are induced by administration of an interactant drug, then the dose of the object drug may need to be altered in order to achieve safe therapeutic concentrations. We consider two likely scenarios
- i) Adding an interacting inducer to an object drug therapeutic regimen results in subtherapeutic concentrations of the object drug: If the increase in metabolic capacity is not recognized when an interactant drug is added to a therapeutic regimen of the object drug and appropriate steps taken, the levels of the object drug may fall to subtherapeutic levels as enzyme levels and metabolic capacity increase.

- ii) Removing an interacting inducer from a therapeutic regimen: Conversely when an individual is stabilized on a multi drug regimen and the interactant inducing drug is removed, the levels of the object drug may increase to toxic levels as enzyme levels and metabolic capacity falls.
- b) The extent of induction caused by drugs on the market is usually no greater than 2-3 fold. However, in some cases the effect can be magnified due to first pass metabolism. This is rarely the case but something to keep in mind.
- c) Mechanisms of Induction using CYP1A2 as an example Induction is the result of binding of a compound (called an inducing agent) to a soluble receptor in the cell cytosol or nucleus. Sometimes there are many binding proteins involved in the process. The final receptor drug complex binds to upstream regions of the gene that codes for a P450 enzymes known as XRE's (xenobiotic response elements) and turns on transcription. The induction of CYP1A2 is best understood.
- i) Binding of inducing agents (TCDD, omeprazole, polycyclic aromatic hydrocarbons) to the AhR receptor leads to increased transcription of the DNA coding for CYP1A2.

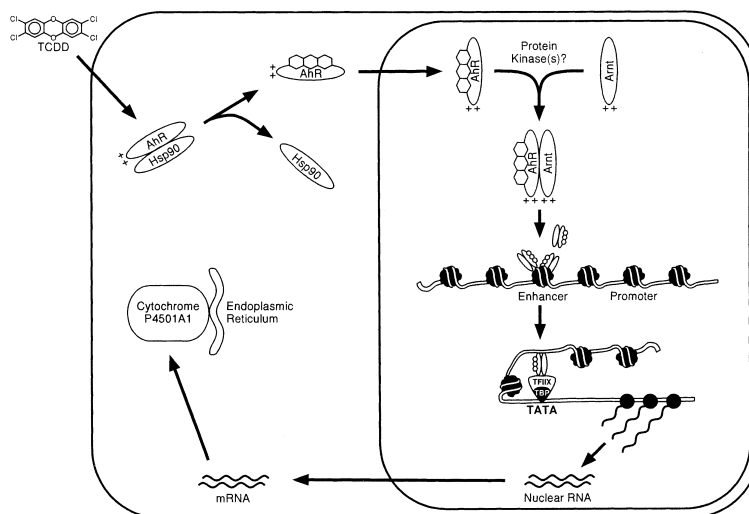


FIG. 6-1. Model for CYP1A1 induction. Reproduced with permission from Whitlock JP, Okino ST, Dong L, et al. Induction of cytochrome P4501A1: a model for analyzing mammalian gene transcription. *FASEB J* 1996;10: 809-817.

CYP1A2 examples: Induction of the CYP1A2 enzymes by PAH's in cigarette smoke has functional consequences for theophylline therapy for asthma, clozapine therapy (antipsychotic) and your coffee bill. Typically one sees up to a two-fold induction of CYP1A2 levels and a maximum increase in metabolic clearance of 2 fold.

- (1) Theophylline, which is used to treat asthma, is cleared from the body mostly due to CYP1A2 dependent metabolism. The mean dose of theophylline that is required to produce therapeutic drug levels is 60% higher in smokers than in the normal population due to induction of CYP1A2. *About 60% of the clearance of theophylline is due to CYP1A2.*
- (2) Clozapine; Antipsychotic: After initiation of clozapine therapy institutionalized patients often quit smoking. In this case the dose of clozapine must be decreased 2-3 fold which means that *most of the metabolism of clozapine is via CYP1A2.*

- (3) One of the benefits of smoking cessation is that caffeine consumption drops thereby lowering one's tab at Starbucks. *Around 90% of caffeine clearance is due to CYP1A2.* A pharmacist I know says the most frequent question he gets at the counter is from people quitting smoking (nicotine patch; etc) is "Why can't I sleep?" Answer is cut down on the coffee.

ii) Other receptors can be activated by inducers to turn on expression of other P450 enzymes.

Receptor Protein(s)	Enzyme Induced
AhR Receptor	CYP1A2
GC (glucocorticoid receptor)	CYP3A4/5
PXR (pregnane X receptor)	CYP3A4/5, CYP2C
CAR-RXR	CYP2C

iii) CYP3A4 Induction:

- (1) Major inducing drugs and herbals are Carbamazepine, Phenytoin, Barbituates, St John's Wort, Dexamethasone, Rifampin
- (2) Many, many object drugs including the statins (simvastatin), oral contraceptive estrogens (ethinyl estradiol), the HIV protease inhibitors (saquinavir).
- (3) Example: Effect of the object interactant drug phenytoin (an anticonvulsant) on the pharmacokinetics of the object drug cyclosporin (an important immunosuppressant) metabolized by CYP3A4.

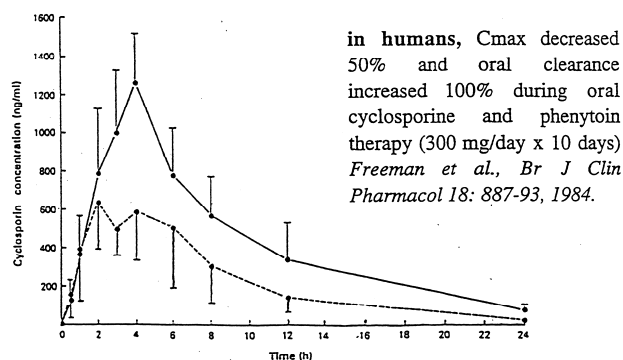
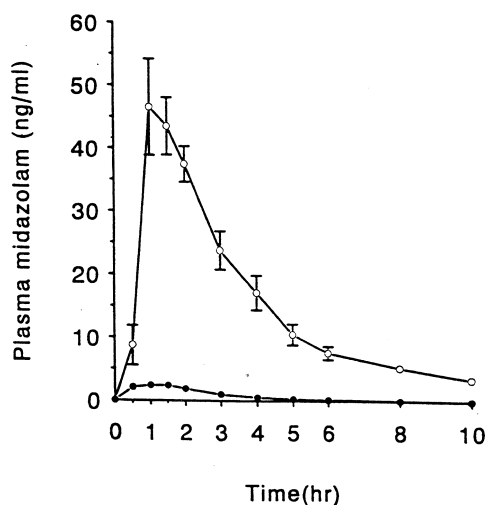


Figure 3 Cyclosporin concentrations measured by h.p.l.c. before (continuous line) and after phenytoin administration (broken line) in whole blood (*)

- (4) The effect of rifampin on bioavailability of an oral dose of midazolam is really large.
 - (a) Notice the dramatic fall in MDZ AUC. This looks like a much bigger effect than the effect of rifampin on MDZ i.v. kinetics. One reason for the magnitude of the effect is that oral MDZ has a big first pass effect (30% of drug reaches systemic circulation).
 - (b) CYP3A in the enterocytes and the liver each contribute to the first pass effect roughly equally.
 - (c) Since these tissues are arranged in series to oral drug getting to the systemic circulation, a two fold induction of CYP3A4 in each tissue would result in a 4 fold drop in bioavailability.

- (d) Thus the magnitude of the effects of induction on active enzyme levels in each of the liver and enterocyte is magnified with respect to systemic bioavailability for orally administered drugs.
- (e) Theoretically, a two fold increase in enzyme levels in each location (would result in a doubling in clearance by each site) would reduce bioavailability by around four fold. Naturally the real world is much more complicated than that but the general concept is valid.

Fig. 1. Plasma concentrations (mean \pm SEM) of midazolam after a 15 mg oral dose following pretreatment with 600 mg rifampin once daily or placebo for 5 days in 10 healthy subjects. *Open circles*, After placebo; *solid circles*, after rifampin.



iv) CYP3A4 Induction by carbamazepine (epilepsy) and oral contraceptives.

Table 2. OC pharmacokinetic parameter estimates during placebo versus CBZ exposure			
	Placebo (n = 10)	CBZ (n = 10)	p-Value
Ethinyl estradiol			
AUC (pg ^h /ml)	1778 (479)	986 (192)	<0.001
Cmax (pg/ml)	147 (48)	95 (23)	0.005
Levonorgestrel			
AUC (ng ^h /ml)	24.7 (12)	13.3 (12)	0.04
Cmax (ng/ml)	2.7 (1.4)	2.1 (1.8)	0.2
AUC calculated from 0–24 h. For ease of interpretation, parameter estimates are presented as means with associated standard deviations. Values were log transformed to generate geometric means, which were compared using a paired Student's t-test.			

- (1) “Our findings confirm a long-standing clinical suspicion; a low-dose OC performs poorly, in terms of ovulation suppression and cycle control, during coadministration of a common dose of CBZ. Some clinicians recommend extended cycle regimens with

OCs containing 50 lg of EE and a shortened pill-free interval.” *Epilepsia* (2011) 52; 243-47.

- (2) Gail Anderson insists that epileptics should not rely on O.C. for birth control. She is very skeptical of simply increasing the dose to match the metabolism due to other effects of the o.c.’s like clotting disorders.
- v) **CYP2C9 Induction:** Inducers include rifampacin, phenytoin, barbituates; Major object drug is warfarin. Below see effect of rifampin (a CYP2C9 inducer and interactant drug) on warfarin levels (an anticoagulant used chronically to inhibit blood clot formation) and pharmacological effect.
- (1) Here a patient is stabilized on warfarin to a desired effect (longer blood clotting time due to reduced prothrombin activity). In the chart the pharmacological effect is given as prothrombin activity.
- (2) A drop from 100% activity (10-11 second clotting time) to the desired effect (20 to 30% of control or a 16 to 20 second clotting time) is achieved by a chronic mean daily warfarin dose of 10 mg.
- (3) Note that warfarin levels (controlled by CYP2C9) plummet when rifampin is added to therapy and the prothrombin activity returns to normal (10 second clotting time). Now the patient will receive no benefit from warfarin unless the dose is adjusted upwards or rifampin is removed.

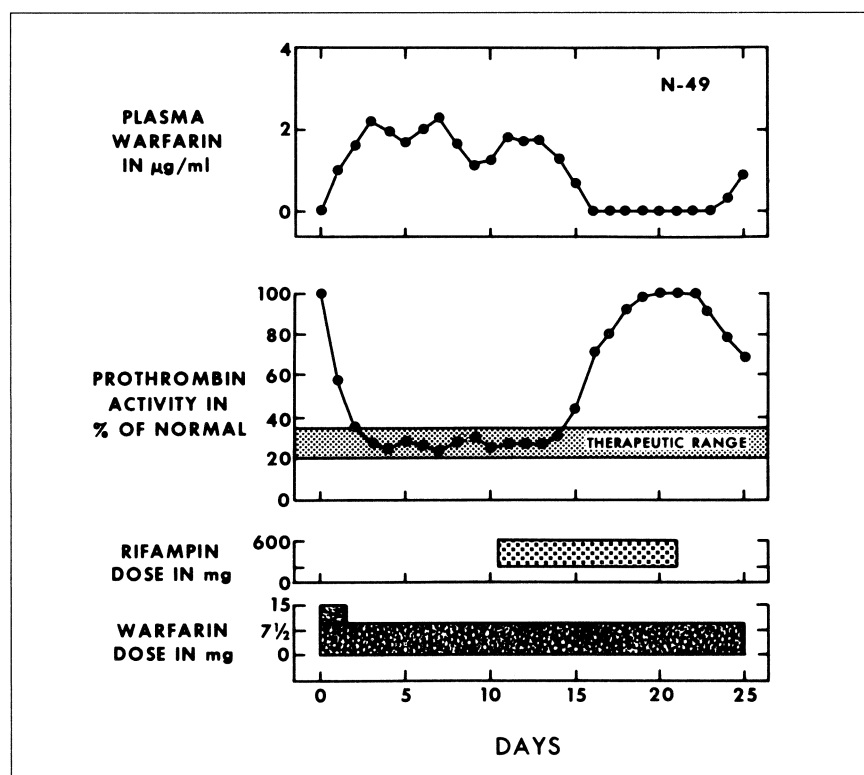


FIGURE 6-6. Plasma warfarin concentration and one-stage prothrombin activity in a healthy adult who received a constant warfarin dose followed by warfarin plus rifampin 600 mg per day. Adapted from reference 99.