



## Review Article

## Drug interactions in human neuropathic pain pharmacotherapy

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**Abstract**

Current practice predicateds the use of multiple drug combinations in the treatment of neuropathic pain. These combinations may be required because of multiple pain symptoms directly arising from neuropathic pathology, other symptoms attributable to the chronicity and severity of the patient's pain or conditions unrelated to their pain. A fear exists that combination drug use or the addition of a new drug to a therapeutic regimen may lead to increased drug toxicity or decreased efficacy. Many of the drug interactions of significance to neuropathic pain physicians involve the cytochromes P450 2D6 and 3A3/4 isoenzymes. Drug interactions should be more predictable based on the knowledge of which compounds induce, inhibit or are metabolized by specific cytochrome P450 enzymes. Mechanisms of induction or inhibition of biotransformation via the P450 hepatic enzyme system are discussed and various inducers, inhibitors and substrates relating to neuropathic pain pharmacotherapy are listed. © 1997 International Association for the Study of Pain. Published by Elsevier Science B.V.

**Keywords:** Neuropathic pain; Drug interactions; Metabolism; Biotransformation; Cytochrome P450

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**1. Introduction**

Drug-drug interactions have increasingly become an important concern for all physicians, including those treating patients with neuropathic pain. Most patients suffering from various forms of neuropathic pain are required to take several medications concurrently to help manage their disease(s) and the accompanying symptoms. Neuropathic pain results from abnormal operation of the pain sensory system after it has been damaged (Gracely et al., 1996). Many patients with neuropathic pain have several distinct spontaneous and evoked sensations of pain in various combina-

tions (Price et al., 1989). Examples of these pains include: persistent burning pain which may arise from spontaneous discharges of damaged C-nociceptor axons, paroxysmal lancinating pains, mechano-allodynia evoked by activation of intact Ab low threshold mechanoreceptive fibers and cold allodynia. A considerable body of evidence from both animal and human models suggests that different kinds of abnormal pains arising from diverse pathophysiologic mechanisms respond differently to various drugs. Evidence for specific drug sensitivity to various forms of neuropathic pain sensations is slowly accumulating in humans (Felsby et al., 1995; Persson et al., 1995; Nikolajsen et al., 1996; Mailis et al., 1997). In clinical practice, based on past experience and case reports, neuropathic pain has been treated for a long time with multiple drug 'cocktails'. These frequently include combinations of tricyclic antidepressants, antiepileptics, antiarrhythmics, calcium channel blockers, adrenergic blocking agents, non-steroidal and steroidal agents,

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muscle relaxants, mild analgesics and narcotics. Given that chronic pain is associated with a multiplicity of constitutional and psychological symptoms such as insomnia, depression, anxiety and fatigue, medications of other classes are often required. These may include: selective serotonin re-uptake inhibitors (SSRIs), benzodiazepines, phenothiazines, etc. In addition, several patients are concurrently taking other medications for reasons unrelated to their pain condition. Some of these medications may include: antacids, H<sub>2</sub>-antagonists, estrogen and thyroid hormone therapy, lipid lowering drugs, antihypertensives, antibiotics, anticoagulants, antihistamines and antidiabetic agents.

General principles governing the administration of a drug targeting specific symptom(s) include (a) the achievement of a therapeutic dose for an adequate period of time, and (b) the relationship of 'targeted' effect versus 'adverse' effect. Therefore, it is imperative that the practicing clinician has not only sufficient knowledge of adequate doses and time frames for administration of any given drug, but be well informed as well about drug interactions that may enhance toxicity or hinder the effectiveness of neuropathic pain medications.

The objective of this article is to review the drug-drug interactions that occur with medications used to treat neuropathic pain with a focus on the cytochrome P450 hepatic enzyme system.

## 2. Background and definitions

A fear exists that combination drug use or the addition of a new drug to a therapeutic regimen may lead to increased drug toxicity or decreased efficacy. Traditionally, practitioners have concentrated on the roles of protein binding, physical incompatibilities, renal excretion, gastrointestinal absorption, and synergistic action of medications in their understanding of the causes of drug interactions. These mechanisms can occasionally be significant as exemplified by the potentially fatal 'serotonin syndrome', which may be caused by the combination of selective serotonin re-uptake inhibitors (SSRIs) and irreversible monoamine oxidase inhibitors (MAOI) (Shulman, 1995). However, recent studies suggest that most of the potentially serious interactions of interest to physicians treating neuropathic pain involve hepatic drug biotransformation pathways catalyzed by the cytochrome P450 group of enzymes (Fig. 1), in particular the 2D6 and 3A3/4 isoenzymes. Cytochrome P450 2D and P450 3A are subfamilies of the cytochrome P450 mixed function oxidase system. The specific molecular mechanisms for some of these interactions have recently been elucidated.

### 2.1. Drug biotransformation

Metabolism refers to the total fate of a drug in the body, including absorption, distribution, biotransformation and

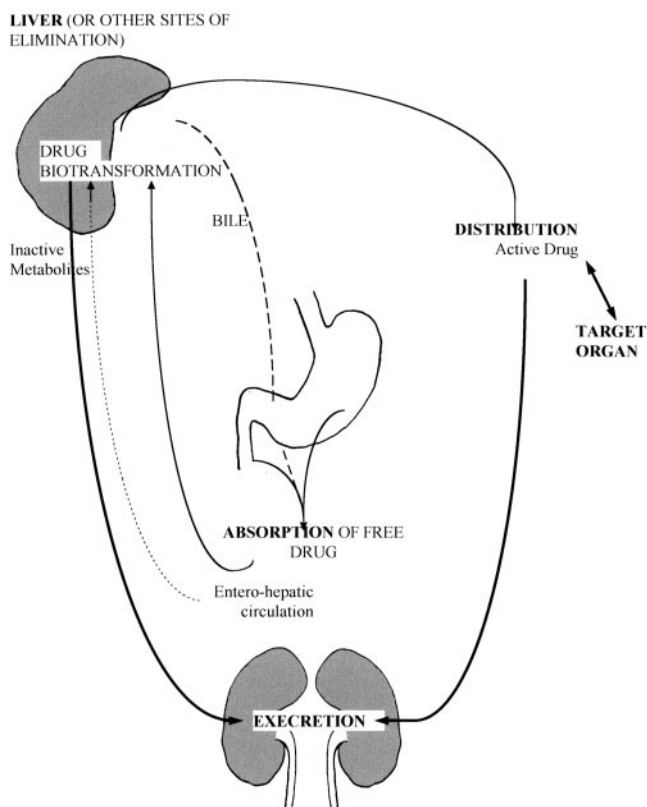


Fig. 1. Drug pharmacokinetics: absorption, biotransformation, distribution and excretion.

excretion. Biotransformation is the chemical transformation of the drug within a living organism, usually by enzyme-catalyzed reactions. Therefore, 'drug metabolism' and 'drug biotransformation' are not synonymous (Kalant, 1989). The essential function of drug biotransformation is to enhance drug hydrophilicity and facilitate its excretion from the body.

Pharmacologic biotransformation reactions may have three different consequences that may affect a drug's activity: (a) activation which occurs when an inactive precursor is converted to a pharmacologically active drug. For example, L-dopa (inactive) is converted to dopamine (active) in the basal ganglia; (b) maintenance of activity which occurs when one active compound is transformed to another active substance, where the new substance can be equal, more or less potent than the original compound. For example, the well-known benzodiazepine diazepam is biotransformed to an active metabolite; and (c) inactivation which occurs when an active compound is converted to inactive product(s). This is seen when the barbiturate pentobarbital is converted to hydroxypentobarbital and glucosylpentobarbital.

Drug biotransformations can occur in almost any tissue in the body and at various subcellular sites within those tissues. The most important organ of biotransformation is the liver. Drug biotransformation reactions have been classified into phase I and phase II processes (Fig. 2). Phase I reactions involving microsomal enzymes, include drug oxidation,

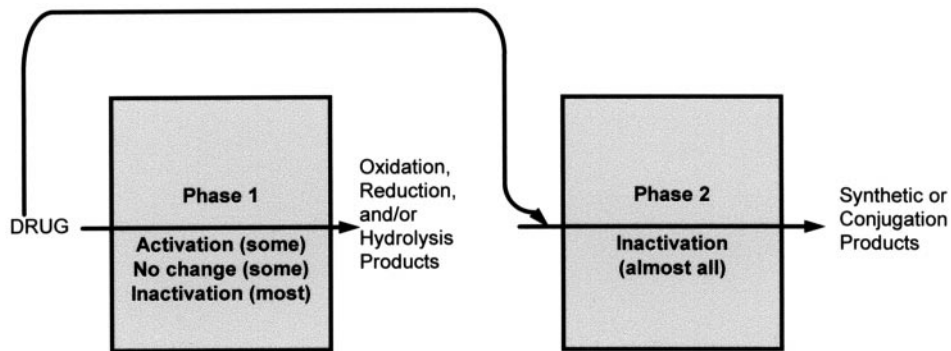


Fig. 2. Sequence and biologic effects of phase 1 and phase 2 drug biotransformation reactions. Adapted from Kalant (1989).

reduction and hydrolysis reactions resulting in intra-molecular changes. Generally the products from phase I reactions may contain hydroxyl, amine, carboxyl, or other groups capable of undergoing further reactions. Phase II reactions that may be catalyzed by microsomal, mitochondrial, and cytoplasmic enzymes or a combination of these, involve extra-molecular changes. These reactions include the conjugation of a drug or drug metabolite with an endogenous substance or some other synthetic reaction to create an even more polar compound that generally has decreased pharmacological activity and toxicity and is more readily excreted.

## 2.2. The cytochrome P450 mixed function oxidase system

The cytochrome P450 mixed function oxidase system consists of the major drug metabolizing enzymes that take part in phase I multi-step drug biotransformation processes involving oxidation and reduction. Cytochrome P450 is a group of heme-containing proteins that differ slightly from each other with respect to molecular weight, carbon monoxide-binding spectra, electrophoretic and immunologic properties, and catalytic activities toward different drugs. The name is derived from the spectral absorbance maximum

produced at or near 450 nm (the best known variant is P448) when carbon monoxide binds to the enzyme in its reduced state (Slaughter and Edwards, 1995). Cytochrome P450 enzymes exist in virtually all tissues, however, they have their highest concentration and activity in the liver. Within hepatocytes, biotransformation occurs at the endoplasmic reticulum. When the liver is fractionated (in vitro), the endoplasmic reticulum is broken up into 'microsomes'. Therefore, cytochromes P450 are sometimes referred to as microsomal enzymes.

Individual purified cytochromes P450 are distinguished on the basis of spectral properties, molecular masses, substrate selectivities and immunoreactivities by monoclonal antibodies that are specific for single epitopes (i.e., antigen sequences in a molecule). An individual cytochrome in the P450 family may have several different epitopes. In general, cytochromes P450 with greater than 40% sequence identity are included in the same family, and those with greater than 55% homology are included in the same subfamily. At least 12 cytochrome P450 gene families and 31 apparently functional cytochrome P450 gene products have been identified in humans along with an additional five apparently non-functional pseudogenes (Fig. 3).

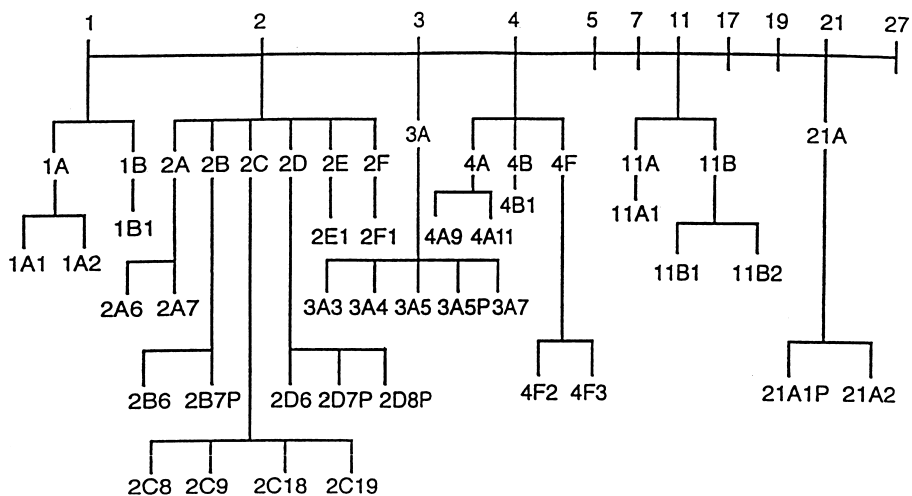


Fig. 3. Cytochrome P450 enzyme tree. Adapted from Riddick (1997).

### 2.2.1. Nomenclature and definitions

The current nomenclature for these enzymes identifies cytochrome P450 enzymes by the root symbol 'CYP' followed by an Arabic number representing the enzyme family, followed by a capital letter designating the subfamily, and ending with an Arabic number which represents the individual enzyme, e.g., CYP3A4 (Riddick, 1997). The final Arabic number is assigned based on numeric order for when the enzyme was discovered. Italics (e.g., *CYP3A4*) are used to denote the gene associated with the enzyme. In humans, enzymes of the CYP1, CYP2 and CYP3 families are responsible for the majority of drug biotransformation reactions and account for 70% of the total P450 content in human liver samples (Slaughter and Edwards, 1995). The most important isoenzymes with respect to drug interactions include CYP1A2, CYP2D6 and CYP3A3/4.

### 2.2.2. The CYP450 1A2 isoenzyme

CYP1A2 has been of clinical interest in part because it catalyzes theophylline, warfarin and caffeine metabolism. CYP1A2 is inhibited by quinolone antibiotics (e.g., ciprofloxacin), and macrolide antibiotics such as erythromycin. Its activity is increased by drugs such as phenytoin, phenobarbital, omeprazole and cigarette smoke.

### 2.2.3. The CYP450 2D6 isoenzyme

The activity of CYP2D6 exhibits a bimodal distribution, suggesting that the gene encoding this enzyme exhibits a polymorphism which leads to clinical phenotypes showing

either extensive or poor drug metabolism. CYP2D6 mediates the metabolism of substrate psychotropic drugs such as amitriptyline, desipramine, nortriptyline and codeine as well as cardiac drugs such as metoprolol, encainide, flecainide and propafenone. CYP2D6 is inhibited by the drugs haloperidol and quinidine (Slaughter and Edwards, 1995) (Table 1). It is important to note that 5–10% of Caucasians are slow metabolizers. Therefore, substrates of the CYP2D6 isoenzyme would have higher serum concentrations in this population.

### 2.2.4. The CYP450 3A subfamily of isoenzymes

The CYP3A subfamily is the most abundant of the human P450 enzyme cytochromes. These isoenzymes account for nearly 30% of the total hepatic cytochromes as well as 70% of gastrointestinal cytochromes. They are responsible for the biotransformation of the widest range of drugs and endogenous human compounds. The most important isoforms are CYP3A3 and CYP3A4. These isoforms are approximately 97% identical in structure, they can not be distinguished on the basis of catalytic activity, their functions may overlap and they have been referred to in the literature as CYP3A3, CYP3A4 or CYP3A3/4. There is some evidence that CYP3A4 may have greater expression than CYP3A3 in the liver (Slaughter and Edwards, 1995). Recent data suggest that a CYP3A5 isoform may also be of clinical importance. It is found in 20–30% of adult livers and is expressed also in the stomach.

In the intestinal tract, P450s are present in the crypt cells

Table 1

Selected list of cytochrome CYP2D6 inhibitors and inducers ('accomplice' drugs) and substrates ('bullet' or 'blank' drugs) (Gelenberg, 1995; Quinn and Day, 1995)

Inhibitors	Inducers	Substrates	Substrates
<i>SSRIs</i>	<i>Anti-tuberculous agents</i>	<i>Anti-arrhythmics</i>	<i>SSRIs</i>
Fluoxetine		Encainide	Fluoxetine
Paroxetine	Isoniazid	Flecainide	Norfluoxetine
Sertraline	Rifampin	Mexilitine	Paroxetine
		Propafenone	
Haloperidol		<i>Anti-psychotics</i>	<i>Tricyclic antidepressants</i>
Quinidine		Clozapine	Amitriptyline
		Haloperidol	Clomipramine
		Perphenazine	Desipramine
		Risperidone	Imipramine
		Thioridazine	Nortriptyline
		Zuclopenthixol	Trimipramine
		<i>Beta blockers</i>	<i>Miscellaneous</i>
		Alprenol	Amiflamine
		Metoprolol	Indoramin
		Propranolol	Phenformin
		Timolol	Terfenadine
			Tomoxetine
		<i>Analgesics</i>	Venlafaxine
		Codeine	
		Dextromethorphan	
		Ethylmorphine	

but the highest concentration is found in enterocytes at the tips of the villi. Enterocyte CYP3A3/4 can cause a significant first pass metabolism of up to 50% of orally administered cyclosporine (Watkins, 1992). There is significant inter-individual variation in the metabolic activity of CYP3A. Differences in the proportions of CYP3A3 versus 3A4 versus 3A5 in the liver and intestinal tract as well as environmental or dietary factors, disease and age contribute to this variation.

### 3. Drug interactions involving P450 enzymes

An improved understanding of the way in which cytochrome P450 enzymes catalyze drug metabolism can improve drug therapy. Drug interactions should be more predictable based on the knowledge of which compounds induce and inhibit or are metabolized by specific P450 enzymes. Although this information may make it possible

to predict an interaction between drugs, the magnitude of interaction and its potential clinical significance are still sometimes difficult to predict solely on the basis of in vitro data and human studies continue to be necessary (Quinn and Day, 1995). Tables 1 and 2 list various substrates, inhibitors and inducers of the CYP2D6 and CYP3A3/4 isoenzymes, which seem to be more relevant to neuropathic pain pharmacotherapy.

#### 3.1. Accomplice/bullet/blank definitions

Drug interactions of hepatic cytochromes consist of enzyme inhibition or induction. Many drugs are either substrates, inhibitors or inducers of CYP2D6 or CYP3A3/4. We group the drugs or foods of concern into two categories that we call 'A' and 'B'. Category 'A' drugs are 'accomplices' in the sense that they help another drug to become more dangerous or less effective. Category 'B' drugs can be either 'bullets' if their concentration increases (which means that

Table 2

Selected list of cytochrome CYP3A3/4 inhibitors and inducers ('accomplice' drugs) and substrates ('bullet' or 'blank' drugs) (Gelenberg, 1995; Quinn and Day, 1995)

Inhibitors	Inducers	Substrates	Substrates
<i>Antidepressants</i>	<i>Anti-convulsants</i>	<i>Anti-arrhythmics</i>	<i>Cancer chemotherapy</i>
Fluoxetine	Carbamazepine	Amiodarone	Cyclophosphamide
Fluvoxamine	Phenobarbital	Lidocaine	Docetaxel
Sertraline	Phenytoin	Propafenone	Paclitaxel
		Quinidine	Tamoxifen
<i>Azoles</i>	<i>Anti-tuberculous agents</i>	<i>Anti-convulsants</i>	<i>HMG-CoA reductase inhibitors</i>
Fluconazole (large doses)	Isoniazid	Carbamazepine	Lovastatin
Itraconazole	Rifampin	Ethosuximide	Simvastatin
Ketoconazole		Phenytoin	
<i>Food</i>	<i>Miscellaneous</i>		<i>Immune suppressive drugs</i>
Grapefruit juice (naringenin)	Clotrimazole	<i>Antidepressants</i>	Corticosteroids
	Dexamethasone	Amitriptyline	Cyclophosphamide
	Griseofulvin	Doxepin	Cyclosporine
<i>Macrolides</i>	Phenylbutazone	Imipramine	Dapsone
Clarithromycin		Sertraline	Tacrolimus
Erythromycin		Nefazodone	
		Venlafaxine	<i>Miscellaneous</i>
<i>Miscellaneous</i>			Acetaminophen
Cimetidine		<i>Antihistamines (non-sedating)</i>	Cisapride
Diltiazem		Astemizole	Codeine
Ethinylestradiol		Fexofenadine	Enalapril
Gestodene		Terfenadine	Erythromycin
Omeprazole			Estrogens
Quinidine		<i>Benzodiazepines</i>	Flutamide
Quinine		Alprazolam	Omeprazole
Ritonavir		Diazepam	Oral contraceptives
Indinavir		Midazolam	Retinoic acid
Tacrolimus		Triazolam	Ritonavir
Valproic acid			Indinavir
		<i>Calcium channel blockers</i>	Theophylline
		Diltiazem	Warfarin
		Felodipine	
		Nifedipine	
		Verapamil	

Notice that substrate drugs (columns 3 and 4) do NOT interact between them. An inhibitor (column 1) or an inducer (column 2) needs a substrate (column 3 or 4) for a drug interaction to occur.

the accomplice is an inhibitor) or 'blanks' if their concentration decreases (i.e., the accomplice is an inducer) (Shapiro et al., 1997). Therefore, category 'A' drugs are either inhibitors or inducers while category 'B' drugs are substrates of the P450 enzymes.

### 3.2. Inhibition of P450 enzymes

The inhibition of drug metabolism is a very important drug interaction as it can lead to increases in plasma drug concentrations, increased drug response and toxicity. Inhibition of a given drug metabolism begins within the first 1–2 doses of administration of the inhibitor (accomplice) drug and is maximal by the time steady state concentration of the inhibitor is achieved. This interaction (in the case of drug inhibition during cytochrome P450 induction, see below) occurs faster than the time needed for new synthesis of the P450 enzyme (Andersen and Feingold, 1995).

The mechanism of enzymatic inhibition can be either competitive or non-competitive. An example of competitive inhibition involves tight binding of accomplice drugs (e.g., cimetidine, ketoconazole and macrolide antibiotics) to the heme moiety of the cytochrome P450 isoenzyme. As long as this specific site of the P450 cytochrome is occupied by the accomplice drug (inhibitor), the bullet drug (substrate) will not be biotransformed. The extent of inhibition of one drug by another will depend on the affinity each compound has for the P450 enzyme (Timbrell, 1991). Non-competitive inhibition occurs when the enzyme is destroyed, inactivated or allosterically changed by the accomplice such that it can no longer metabolize the original substrate. For example, drugs like chloramphenicol and spironolactone can cause inhibition of another drug's metabolism by forming suicidal reactive intermediate metabolites that inactivate cytochromes (Riddick, 1997) metabolizing the latter. Another example involves 17  $\alpha$ -acetylenic steroids such as ethinylestradiol or the progestin gestodene which decrease the rate of ethinylestradiol elimination after multiple doses by destroying cytochrome P450 3A4. This occurs due to binding of the ethinyl substituent with the cytochrome and the production of an inactive intermediate radical that has lost its heme iron atom and can no longer catalyze drug metabolism (Murray, 1992).

Of interest in neuropathic pain pharmacotherapy are substrates such as mexiletine, tricyclic antidepressants, haloperidol, propranolol, codeine and dextromethorphan that are metabolized by CYP2D6 isoenzymes (Table 1). An important class of drugs which inhibit these isoenzymes are SSRIs. In contrast, CYP3A3/4 isoenzymes (Table 2) metabolize substrates such as carbamazepine, sertraline, midazolam, cisapride, terfenadine, astemizole and nifedipine and are inhibited by drugs such as imidazole-triazole antifungals, oral contraceptives, cimetidine and macrolide antibiotics such as erythromycin and clarithromycin (Murray, 1992).

An illustrative example of an inhibitory drug interaction

involving CYP3A3/4 (even if this is not of direct interest to neuropathic pain pharmacotherapy) is the occurrence of a serious cardiac arrhythmia associated with co-administration of the 'bullet' drug terfenadine and the 'accomplice' drug ketoconazole. A case of syncope and Torsades de Pointes was reported in a 39-year-old woman who began a course of terfenadine and then started ketoconazole on the eighth day of treatment (Monahan et al., 1990). Two days after the introduction of the latter she developed syncopal symptoms, prolongation of her QT interval on electrocardiogram as well as Torsades de Pointes. Serum concentrations of terfenadine and its main metabolite showed excessive levels of the former and proportionately reduced concentrations of the latter, suggesting inhibition of metabolism. It was concluded that ketoconazole inhibition of terfenadine metabolism led to cardiotoxic levels of this drug in the case reported above. More recently, healthy volunteers were given terfenadine and after achieving a steady state concentration, ketoconazole was added (Honig et al., 1993). After the addition of ketoconazole, all subjects had detectable levels of unmetabolized terfenadine and QT prolongation. Unmetabolized terfenadine was shown to be a blocker of potassium current in feline ventricular myocytes which may explain its cardiotoxicity in humans.

Peripheral edema due to an interaction between nifedipine (a calcium-channel blocker used in the treatment of Raynaud's phenomena and the vasoactive manifestations

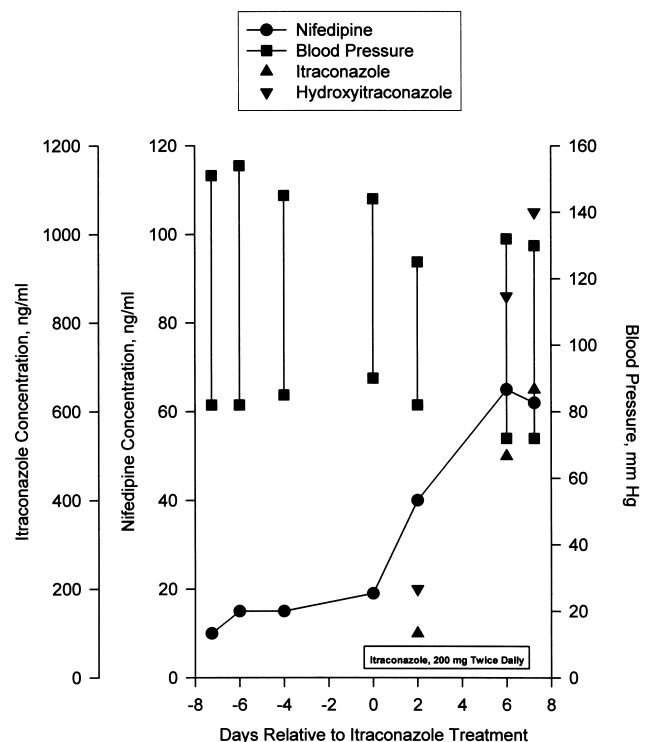


Fig. 4. Itraconazole-nifedipine interaction. Drug concentrations and blood pressure before and during itraconazole therapy. Adapted with permission from Taylor et al. (1996).

of complex regional pain syndromes) and itraconazole has been recently reported (Tailor et al., 1996). The suspicion that itraconazole (an ‘accomplice’ drug) could inhibit the metabolism of nifedipine (a ‘bullet’ drug) was confirmed by obtaining serum levels of nifedipine, itraconazole and hydroxy-itraconazole (the active metabolite of itraconazole) before and after the administration of the latter (Fig. 4). The authors recommended that patients receiving both azole/triazole antifungals and calcium channel blockers should be monitored for side-effects such as leg edema and hypotension due to increased serum concentration of the calcium channel blocker (Tailor et al., 1996).

Of interest is a novel food-drug interaction involving the co-administration of grapefruit juice with substrates of CYP3A3/4 isoenzymes such as felodipine, nifedipine, cyclosporine and terfenadine (Benton et al., 1996). Grapefruit juice contains certain bioflavonoids (e.g., naringenin, kaempferol and quercetin) that can inhibit oxidation reactions occurring in gastrointestinal wall CYP3A3/4 enzymes (Gibaldi, 1992). This effect is maximal if grapefruit juice is ingested 30–60 min prior to drug administration. However, since grapefruit juice is not a licensed pharmaceutical product with a defined specification for all its constituents, the flavonoids in various grapefruit products may vary by as much as sixfold (Tailor et al., 1996). Orange juices usually do not contain these bioflavonoids and therefore do not inhibit metabolism.

### 3.3. Induction of P450 enzymes

Many drug biotransforming enzymes are able to increase in amount and activity in response to substances known as inducers. Induction of the rate of drug biotransformation results in a decrease in parent drug concentration and either decreased pharmacologic effect or increased toxicity (if reactive metabolites are formed). For example, cyclophosphamide is hepatically converted to active metabolites. If a patient is receiving simultaneously phenobarbital (an inducer of hepatic enzymes), he is likely to have significantly higher serum concentrations of the principal metabolite of cyclophosphamide. Conversely, isoenzyme induction could potentially lead to a decrease in drug metabolism and an increase in parent drug levels if the level of one isoenzyme is increased at the expense of the isoenzyme that normally metabolizes the compound in question (Timbrell, 1991). The onset and offset of enzyme induction is gradual since (a) the induction phase depends upon the accumulation of the particular inducing agent and subsequent synthesis of the new enzyme, while (b) offset depends upon elimination of enzyme-inducing drug and decay of the increased enzyme stores.

Many molecular mechanisms for enzyme induction have been characterized. The most common means of regulation is increased DNA transcription. However, post-transcriptional mechanisms such as RNA processing, mRNA stabilization, translational efficiency, protein stabilization and

decreased heme degradation have been identified as well (Timbrell, 1991; Riddick, 1997).

Accomplice drugs like rifampin, dexamethasone and griseofulvin and anticonvulsants, such as carbamazepine, phenobarbital and phenytoin, induce members of the CYP3A subfamily. Rifampin indeed is the most potent inducer of cytochrome CYP3A in clinical use. Because some estrogens are metabolized by CYP3A3/4, induction by rifampin explains why women treated with this drug may experience oral contraceptive failure (Shenfield, 1993). In reality, any enzyme inducer can potentially result in oral contraceptive failure. Several examples of where CYP3A3/4 enzyme inducers may decrease serum concentrations of various other medications are included in Table 2.

Carbamazepine, an antiepileptic with a myriad of drug interactions, potentially can decrease the effect of various medications by decreasing their serum concentrations or it can expedite the biotransformation of a drug to an active metabolite. For example, after 2 weeks of treatment with carbamazepine, the mean serum concentration of clobazam, a benzodiazepine, decreased by 61% (Levy et al., 1983). Meanwhile, the mean serum concentrations of norclobazam, the principal metabolite of clobazam, increased by 44%. A similar interaction has been described with diazepam. As these benzodiazepines have mostly active metabolites, a decrease in clinical effect may not be evident. However, if the metabolites are not active, a decrease in effect is likely to be seen. For example, midazolam concentration after oral ingestion is significantly reduced in the presence of carbamazepine or phenytoin (Backman et al., 1996) (Fig. 5). This was attributed to the induction of CYP3A4 mediated first pass metabolism.

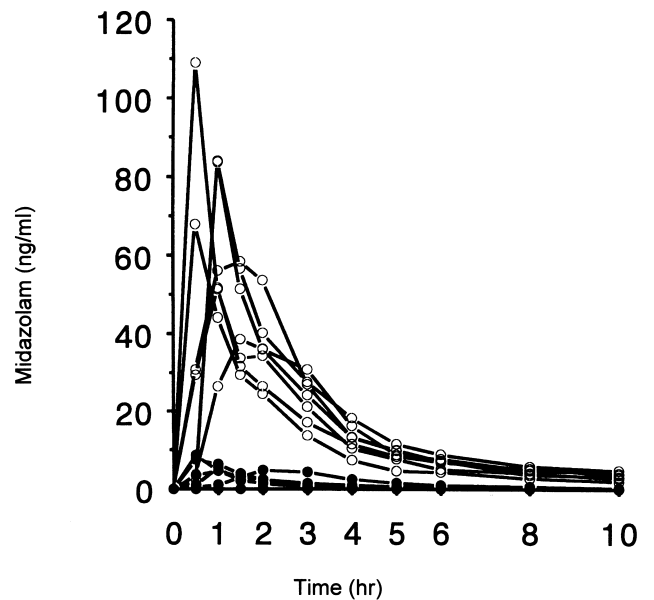


Fig. 5. Plasma midazolam concentrations are dramatically reduced after a 15-mg oral dose of midazolam in six patients with epilepsy taking carbamazepine or phenytoin (solid circles) when compared to seven healthy control subjects (open circles). Adapted with permission from Backman et al. (1996).

Table 3

Common drug interactions during pharmacotherapy of neuropathic pain

Drug class	May interact with	Potential result	Implication for management
<i>Adrenergic blockers</i>	Amphetamines, anorexiant (except, fenfluramine), chlorpromazine, ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, tricyclic antidepressants	Anti-hypertensive effect antagonized and control of blood pressure lost.	Avoid these combinations, especially oral cold preparations. Use an antidepressant with little or no effect on noradrenaline (e.g., SSRI).
<i>Anesthetics, general (ketamine)</i>	Diazepam, hydroxyzine, secobarbital	Prolonged recovery time by 30–40% with use of these agents as premedications. Severe hypertension and tachycardia.	Be aware of extended recovery time when combination used for short surgeries. Avoid combination. May be controlled with beta blockers.
	Thyroid hormones		
<i>Analgesics (ASA and NSAIDs)</i>	Alcohol	Potential of aspirin-induced gastric mucosal damage and prolongation of bleeding time.	Caution patient to avoid alcohol and ASA, especially in the long term.
	Corticosteroids	Reduced salicylate concentrations.	Monitor pain relief and adjust salicylate concentration when adding or withdrawing corticosteroids.
(Fentanyl, methadone)	CBZ, phenytoin, rifampin (plus other enzyme inducers)	Decreased plasma concentrations and possible symptoms of opioid withdraw (if on maintenance methadone).	Titrate fentanyl to required anaesthetic effect. May need to increase methadone dose. Consider using alternate anti-epileptic (e.g., valproic acid) where there is no induction of P450 enzymes).
Opioids (morphine)	Alcohol, anti-psychotics, anti-anxiety agents, thiopental, sedating anti-histamines (e.g., hydroxyzine diphenhydramine)	Increased CNS depressant effects.	Use lower doses of either opioid or interacting drug. Inform patient of possible effect on performance tasks.
	Cimetidine	Potential for increased plasma concentrations and duration of action of opioid.	Avoid combination if possible. Consider alternate H <sub>2</sub> antagonist. Antagonize opioid effect with naloxone if necessary.
	TCA	Prolongation of and potential for adverse effects (sedation), depressant effects.	Start TCA at low dosage and increase while monitoring for adverse effects (sedation).
<i>Anti-anxiety agents benzodiazepines (chloral hydrate) (glutethimide)</i>	Alcohol, analgesics (strong) <sup>a</sup> , antidepressants <sup>a</sup> , antihistamines (some), anti-psychotics, beta blockers, erythromycin	Enhanced CNS depressant effects, either by central effect or inhibition of metabolism resulting in increased concentration of drug concerned.	Avoid these combinations, if possible. May need to reduce dose of either agent. Monitor and inform patient of increased drowsiness potential. Use short-term, solely glucuronidated benzodiazepines (oxazepam, lorazepam or temazepam) whenever possible.
(Diazepam, midazolam)	Cimetidine, ranitidine, diltiazem, verapamil, itraconazole, ketoconazole	Increased plasma concentrations of midazolam and sometimes diazepam. Can lead to a higher level, as well as longer duration of sedation.	Avoid use of combination. Use short-term, solely glucuronidated benzodiazepines (oxazepam, lorazepam, or temazepam) if possible.
	Barbiturates, CBZ, phenytoin, other P450 inducers	Decreased benzodiazepine plasma concentrations.	Monitor patient's response to benzodiazepines and adjust dosage accordingly. (No decrease in clinical effect is likely with clobazam or diazepam as they have active metabolites). Watch for withdrawal from drugs like midazolam. Use short-term, solely benzodiazepines (oxazepam, lorazepam or temazepam) whenever possible.
<i>Anti-arrhythmics (mexiletine, disopyramide, quinidine)</i>	Barbiturates, CBZ, phenytoin, other P450 inducers Quinidine, theophylline, adrenergic blockers <sup>a</sup> , opioids <sup>a</sup>	Decreased anti-arrhythmic plasma concentration. Increased plasma mexiletine concentrations in some patients.	Monitor patient's plasma concentrations and adjust dosage accordingly. Avoid these combinations or monitor plasma mexiletine.
<i>Anti-depressants, tricyclic (e.g., desipramine amitriptyline amoxapine)</i>	Epinephrine-containing local anesthetics, norepinephrine SSRIs, (e.g., fluoxetine paroxetine, sertraline, fuvoxamine), cimetidine, quinidine	Prolonged pressor response, possible arrhythmia. Use plain local anesthetics. Marked increase in plasma concentrations of TCA, may be associated with toxicity.	Use plain local anesthetics. Decrease dose of TCA (if still required). Monitor for toxicity to TCA. Caution with all drugs biotransformed by CYP2D6 and CYP3A3/4 as SSRIs inhibit these enzymes. Consider alternate H <sub>2</sub> antagonist.

Table 3 (continued)

Drug class	May interact with	Potential result	Implication for management
<i>Anti-diabetic agents</i> (sulphonylureas)	Barbiturates, CBZ, phenytoin, other P450 inducers	Decreased tricyclic plasma concentration.	Titrate TCA dose to response. Patients on P450 inducers may require higher doses of TCAs.
	Barbiturates, phenytoin, rifampin, CBZ (and other, P450 enzyme inducers)	May make diabetic control more difficult by decreasing the hypoglycemic effect of the sulphonylurea.	Of considerable concern with medications cleared primarily by the liver (tolazamide, tolbutamide, acetohexamide, glibenclamide). Monitor blood glucose when starting, modifying, or withdrawing an enzyme inducer. Consider using benzodiazepines as an alternative.
	Corticosteroids	May worsen diabetic control.	Monitor blood glucose when starting, modifying, or withdrawing any corticosteroids.
<i>Anti-epileptic drugs</i> barbiturates (e.g., phenobarbital, primidone)	Phenytoin	Decrease in plasma concentration of phenobarbital by 30% over 1–4 weeks.	Monitor plasma concentrations of phenobarbital (or primadone) and phenytoin. Adjust dosage as required.
	VPA	Increased plasma concentrations of phenobarbital with marked sedation.	Reduce dose of phenobarbital (or primadone) when valproic acid is added to a stable regime.
(Carbamazepine; CBZ)	TCAs <sup>a</sup> , beta blockers <sup>a</sup> , corticosteroids <sup>a</sup>	Variable increase in plasma CBZ concentration by up to 30%.	Consider alternate H <sub>2</sub> antagonist.
	Cimetidine	Marked increase in plasma CBZ concentration.	Avoid use of dextropropoxyphene for pain relief for >1 day. Consider other analgesics.
	Dextropropoxyphene	Marked increase in plasma CBZ concentration with toxicity.	Monitor CBZ serum levels when either diltiazem or verapamil is added to a stable regimen.
	Diltiazem, verapamil	Marked increase in plasma CBZ concentration with toxicity.	Avoid use of these combinations if possible. Substitute alternate antibacterial. Monitor CBZ serum concentrations adding or withdrawing these macrolides.
	Erythromycin, clarithromycin	Marked increase in plasma CBZ concentration with toxicity.	Monitor both CBZ and phenytoin plasma concentrations when commencing, altering/withdrawing either drug. Monitor for CBZ toxicity despite 'therapeutic' plasma CBZ concentrations.
	Phenytoin	Decreased plasma CBZ concentrations with concurrent increase in plasma CBZ-10,11-epoxide concentrations.	Increase dose of lamotrigine by up to 50%. Monitor for CBZ toxicity despite 'therapeutic' plasma CBZ concentrations.
	Lamotrigine	Decreased lamotrigine concentrations. Possible increase in CBZ-10,11-epoxide concentrations.	Monitor CBZ and VPA serum concentrations when either drug is added, altered or withdrawn from a stable regimen.
(Phenytoin)	VPA	Marked increase in plasma CBZ and CBZ-10,11 epoxide concentrations with toxicity. Marked decrease in VPA concentrations by up to 50%.	
	Beta blockers <sup>a</sup> , corticosteroids <sup>a</sup> , fentanyl, methadone <sup>a</sup> , TCAs <sup>a</sup> , benzodiazepines <sup>a</sup>	Marked increase in phenytoin concentration.	Monitor plasma phenytoin concentrations and adjust dose accordingly if this combination can not be avoided.
	Cimetidine, fluconazole, omeprazole	Decreased lamotrigine concentrations. Marked but temporary increases in free (unbound) phenytoin concentrations. As well as, decrease of VPA concentration of up to 50%	Increase dose of lamotrigine by up to 50%. Monitor plasma concentrations of phenytoin and VPA when either drug is added, modified or withdrawn. May need to adjust dosages of both anti-epileptics. Phenytoin dose may need to be decreased initially.
	Lamotrigine		
	VPA		
	Anti-diabetic agents <sup>a</sup> , antifungals <sup>a</sup> , barbiturates <sup>a</sup> , CBZ <sup>a</sup> , corticosteroids <sup>a</sup> , TCAs <sup>a</sup>		

Table 3 (continued)

Drug class	May interact with	Potential result	Implication for management
(Valproic acid; VPA)	Erythromycin, isoniazid	Increased plasma VPA concentrations.	Monitor VPA plasma concentrations when either erythromycin or isoniazid is added, modified or withdrawn from a stable regimen. Consider alternative antiretrovirals.
	Lamotrigine	Increased lamotrigine concentrations.	Decrease dose of lamotrigine by up to 50%.
<i>Anti-fungals</i> (ketoconazole) (itraconazole)	Barbiturates <sup>a</sup> , CBZ <sup>a</sup> , phenytoin <sup>a</sup> Antacids, H <sub>2</sub> antagonists, sucralfate, didanosine	Absorption of ketoconazole and itraconazole significantly decreased. Possible ineffective anti-fungal therapy.	Use fluconazole if possible (no reported interaction). May need to give higher doses of anti-fungal. Give anti-fungal with acidic beverage (e.g., Coca Cola) and not concurrently with antacids or sucralfate.
	Barbiturates, phenytoin, rifampin, CBZ (and other P450 enzyme inducers), anti-anxiety agents <sup>a</sup> , antihistamines <sup>a</sup>	Decreased plasma concentrations of ketoconazole and itraconazole with possible treatment failure.	Avoid these combinations if possible or use fluconazole (no reported interaction). May need higher doses of anti-fungal.
<i>Antihistamines</i> (terfenadine, atemazole)	Erythromycin, clarithromycin, fluoxetine, itraconazole, ketoconazole	Marked increased plasma concentrations of terfenadine and astemizole with resultant QT prolongation and risk of potentially fatal ventricular arrhythmias.	Avoid these combinations. Substitute cetirizine or loratidine (or sedating anti-histamine) for terfenadine or astemizole. Or consider alternative antibiotic, anti-fungal (fluconazole, amphotericin B).
<i>Beta blockers</i> (propranolol, metoprolol, alprenolol)	Barbiturates, CBZ, rifampin, anti-anxiety drugs <sup>a</sup>	Decreased plasma concentrations of propranolol, metoprolol, and alprenolol.	Watch for decreased beta-blocker response. Consider using nadolol, atenolol, or sotalol as they are less likely to be affected.
<i>Corticosteroids</i> (dexamethasone, hydrocortisone, methyl-prednisolone, prednisone, prednisolone)	Barbiturates, phenytoin, rifampin, CBZ (and other P450 enzyme inducers)	Enhanced metabolism of corticosteroids. Efficacy of systemic steroid reduced.	Increased steroid dosage may be needed, particularly in longer acting steroids (e.g., dexamethasone). Avoid occasional use of barbiturates, use benzodiazepines as alternative.
<i>Muscle relaxants</i> non-depolarizing (tubocurarine, pancuronium, vecuronium, atracurium)	Aminoglycosides, amphotericin B, clindamycin, cyclosporin, furosemide, magnesium infusions, quinidine, tetracycline	Neuromuscular blocking activity may be increased.	Avoid combination if possible. If combination used, anticipate prolongation of block.

<sup>a</sup>Indicates the interaction has also been discussed under the drug class that precedes the asterisks. Specific medications listed under drug class (in brackets) indicate a known interaction in the literature (Quinn and Day, 1995) with drugs that can be used for the treatment of, or in conjunction with, other medications in patients with neuropathic pain. Drugs have been arranged alphabetically by drug class. This table is not a comprehensive list of drug interactions as comprehensive tables are available from other references (Quinn and Day, 1995).

Persistent cytochrome P450 induction by anticonvulsants and alcohol alone or in combination, may also precipitate crises of porphyria due to increased demand for heme and excessive accumulation of intermediates in the heme biosynthetic pathway (Parkinson, 1996).

Table 3 lists drug classes commonly used in patients with neuropathic pain and their potential interactions with multiple medications. While far from being complete and comprehensive (as detailed tables are available from other references), the table details some of the commonest and significant drug interactions of interest to the practicing physician. While this paper has focused on the P450 enzyme interactions, this table outlines interactions occurring by some other mechanisms as well.

#### 4. Conclusion

Current practice calls for the use of multiple drug combinations in the treatment of neuropathic pain. These combinations may be required because of multiple pain symptoms directly arising from neuropathic pathology, other symptoms attributable to the chronicity and severity of the patient's pain or conditions unrelated to their pain. Knowledge of drug metabolism and the interactive role of cytochrome P450 enzymes for old and newly developed drugs continues to proliferate at a fast pace. Prescribers of pain medications should keep abreast of these developments in order to maximize the safety and efficacy of their patients' treatment.

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