NEW ANTIDEPRESSANTS AND THE CYTOCHROME P_{450} SYSTEM: FOCUS ON VENLAFAXINE, NEFAZODONE, AND MIRTAZAPINE

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Objective: This review critically evaluates recent information on the cytochrome P_{450} system, with an emphasis on drug interactions involving antidepressant medications, particularly venlafaxine, nefazodone, and mirtazapine. Methods: International literature on the cytochrome P_{450} system and related drug interactions from 1995–1997 were critically examined. Results: Venlafaxine, nefazodone, and mirtazapine have different effects on the cytochrome P_{450} system. In vitro, venlafaxine is a weaker CYP2D6 inhibitor than most of the selective serotonin reuptake inhibitors (SSRIs) by a factor of 1–3 orders of magnitude. In vivo drug interaction studies generally confirm in vitro results. However, some exceptions exist. The clinical significance of such interactions remains unknown. Venlafaxine had minimal or no demonstratable inhibition of CYP1A2, CYP3A4, or CYP2C. Nefazodone is a potent inhibitor of CYP3A4 and is therefore absolutely contraindicated with concurrent administration of terfenadine, astemizole, and cisapride. It is a weak inhibitor of CYP1A2, 3A4, and 2D6. A metabolite of nefazodone, mCPP, is a weak and probably clinically insignificant inhibitor of CYP2D6. Mirtazapine has minimal inhibitory effects on CYP1A2, CYP3A4, and CYP2D6 in vitro. Little is known about its interactions with other drugs. Conclusions: With the addition of the latest antidepressant medications, the clinician may now choose antidepressants with little liability for drug–drug interactions. Venlafaxine and mirtazapine are associated with a lower risk of clinically significant drug interactions than SSRIs. Nefazodone is a potent inhibitor of CYP3A4 and therefore may not be suitable for all patient populations. It is, however, a much weaker CYP2D6 inhibitor than the SSRIs. More studies are needed to assess more accurately and precisely the risk of such untoward drug–drug interactions with these novel antidepressants, particularly in more diverse ethnic patient populations. Depression and Anxiety, Volume 7, Supplement 1:24–32, 1998. *© 1998 Wiley-Liss, Inc.*

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INTRODUCTION

Drug–drug interactions are well known to result in untoward and even serious side effects. These may result in undue pain and suffering, and increased hospital stays, office visits, costs, and comorbid complications. They can obviously also interfere with the therapeutic relationship between the patient and physician as well as foster noncompliance, with all of its attendant risks. Of course, not every drug–drug interaction is serious. Some may even be utilized to the patient's benefit, by maximizing therapeutic effects

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and minimizing unwanted "side effects." The vast majority of drug interactions, however, are neither helpful nor harmful. Pharmacokinetic alterations frequently do not translate into significant pharmacodynamic effects. The task for the clinician is to discriminate between those drug interactions which are clinically meaningful and those which are not, and to address these interactions appropriately.

A great body of research has focused on the potential for drugs, particularly antidepressants, to interact with one or another hepatic cytochrome P_{450} isoenzyme. Much of this research has been comprehensively reviewed elsewhere (Nemeroff et al., 1996; Richelson, 1997; Ershefsky, 1996). As information on this subject grows, new research must be incorporated with old. This review scrutinizes the evidence as to whether the newest antidepressants inhibit activity of the cytochrome P_{450} isoenzymes and provides clinically relevant recommendations for their use in clinical situations in which drug interactions might occur. We begin with a review of the different variables by which drug interactions are measured, followed by a synopsis of each of the relevant cytochrome P_{450} isoenzymes. Next, the effects of venlafaxine, nefazodone, and mirtazapine on the hepatic cytochrome P_{450} system are discussed, with a focus on clinical practice. Our goal is to encourage the rational use of antidepressants, allowing clinicians to predict and avoid clinically significant interactions and thereby treat these severe psychiatric disorders.

MATERIALS, METHODS, AND RESULTS

PRINICIPLES OF DRUG INTERACTIONS

Drug–drug interactions occur by a variety of mechanisms, both pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions involve the actions of drugs at receptor sites. For example, the coadministration of most antidepressant medications with MAO inhibitors overactivates central 5HT receptors in a potentially life-threatening clinical presentation termed "the serotonin syndrome." Pharmacokinetic interactions, conversely, involve alterations in the disposition of drugs within the body. These can occur at any stage of drug absorption, metabolism, distribution, or elimination. This paper focuses predominantly on pharmacokinetic interactions, specifically cytochrome P_{450} metabolism, which mediates oxidation reactions.

Isoenzyme interactions involve a number of independent variables. Typically, a drug's affinity to an isoenzyme is considered to be a relative measure of its inhibitory potential. Drugs with high affinity (low K_i) are more likely to bind to isoenzyme sites than are drugs with low affinity (high K_i). When two drugs are given together, the drug with the higher affinity will competitively inhibit the binding of the lower affinity drug. Of course, other variables should be considered as well. These include peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the curve (AUC), minimum plasma concentration (C_{min}), and half-life ($t_{1/2}$). These variables in turn may be dependent on such factors as dosage and duration of treatment, protein binding, and distribution.

Alterations in any one of these variables may or may not be clinically significant. Thus, in vivo studies are ultimately essential to our understanding of drug–drug interactions. However, these studies are frequently performed using a single dose administered to approximately 18–20 healthy male subjects under tightly controlled conditions. These studies may not account for distribution kinetics (alpha elimination), accumulation of metabolites, or differences due to age, gender, race, physical health, and other conditions. Consequently, such in vivo results may not correspond well to findings in clinical settings.

Clinical significance itself depends on several variables. The therapeutic index of the substrate is of particular importance. For drugs such as warfarin and digoxin, with low therapeutic indices, small changes in plasma concentration can be of concern. Therefore, heightened vigilance is warranted when using these agents concurrently with drugs which are known or suspected cytochrome P_{450} isoenzyme inhibitors.

Genotypic polymorphism is also important, for it renders some people more vulnerable to the effects of drug interactions. For example, about 5–10% of the Caucasion population are poor metabolizers of CYP2D6, and higher percentages of other ethnic groups may fall into this category. In these individuals, substrates of CYP2D6 are metabolized more slowly than in extensive metabolizers, increasing the potential for harmful side effects. Ironically, individuals with the genetic polymorphism resulting in a complete lack of CYP2D6 have no enzyme and therefore cannot show any reduction in its activity. As such they are immune to CYP2D6 inhibitors (vide infra).

The effects of drug interactions are commonly seen when medications are initiated, increased, decreased, interrupted, or discontinued. Such medication changes often occur without the physician's knowledge. For reasons of carelessness, forgetfulness, confusion, or misunderstanding, as well as for psychodynamic reasons, patients may not take medications as prescribed. Some patients simply cannot afford their medications and take them intermittently at best. Moreover, patients may have multiple physicians prescribing medications of which other physicians are unaware. Unfortunately, noncompliance and unintentional polypharmacy are common, and may contribute to untoward drug–drug interactions.

Fortunately, many if not most drugs have multiple metabolic pathways. Thus, even if one isoenzyme is inhibited, drug metabolism may proceed along alternate pathways. These alternate pathways most likely

account for the differences sometimes found between in vitro and in vivo studies.

CYP2D6. CYP2D6 has been the most extensively studied of the cytochrome P_{450} isoenzymes. Approximately 5% to 10% of Caucasians and up to 2% of persons of Asian and African descent lack this enzyme as a result of an autosomally recessive inherited defect in its expression. There are nine mutant forms of the CYP2D6 gene which are either inactive or poorly active (Kroemer and Eichelbaum, 1995). Individuals who are poor metabolizers will exhibit greater bioavailability, greater plasma concentrations, prolonged elimination half-lives, and possibly exaggerated pharmacologic response from standard doses of drugs that are metabolized by CYP2D6 (Eichelbaum and Gross, 1990). When drugs that inhibit P_{450} isoenzymes are administered with drugs that are metabolized by this enzyme, extensive metabolizers are, in effect, converted to poor metabolizers. The extent of the conversion will depend on the affinity of the inhibitor for the enzyme, the dose of the inhibitor, and the length of therapy.

CYP2D6 metabolizes many different classes of drugs, including antidepressants, antipsychotics, β-adrenergic blockers, type 1C antiarrhythmics, dextromethorphan, codeine, and some chemotherapeutic agents.

Drugs metabolized primarily by CYP2D6 which have a low therapeutic index should be initiated at the low end of the dose range if coadministered with potent CYP2D6 inhibitors, such as fluoxetine (Medical Economics, 1997b). Drugs of greatest concern are flecanide, vinblastine, carbamazepine, and tricyclic antidepressants (TCAs). Because of its long half-life, fluoxetine in particular can inhibit CYP2D6 metabolism for 5 weeks after its discontinuation.

The relative potency of CYP2D6 inhibition among antidepressants is: paroxetine ≥ norfluoxetine ≥ fluoxetine > sertraline > fluvoxamine > venlafaxine ≥ nefazodone > mirtazapine (Richelson, 1997). There is no available date on bupropion. Secondary TCAs, thioridazine, and haloperidol may also inhibit CYP2D6.

CYP3A4. CYP3A4 is frequently considered the most clinically important P_{450} isoenzyme, comprising a sizable portion of the total P_{450} content of the liver. There is no evidence that CYP3A4 exhibits genetic polymorphism.

CYP3A4 metabolizes a broad range of compounds, including triazolobenzodiazepines (e.g., alprazolam), terfenadine, astemizole, cisapride, carbamazepine, sertraline, TCAs, calcium channel blockers, cyclosporin, erythromycin, steroids, codeine, quinidine, lidocaine, and others.

Nefazodone and fluvoxamine are contraindicated to be coadministered with terfenadine, astemizole, and cisapride because they are both potent CYP3A4 inhibitors (Medical Economics, 1997a,c). Although it has not been unequivocally demonstrated that these drug combinations could result in mortality, the potential is there based on the fact that ketoconazole, a very potent CYP3A4 inhibitor, blocks the metabolism of these drugs. Increases in their plasma concentrations are known to cause prolonged QT intervals, and have also been associated with ventricular arrhythmias, torsades de pointes subtype, which is sometimes fatal. Moreover, both nefazodone and fluvoxamine have warnings about being coadministered with certain benzodiazepines because of their propensity to increase their plasma concentrations.

The relative potency of CYP3A4 inhibition among antidepressants is: nefazodone > > fluvoxamine > norfluoxetine > paroxetine ≥ desmethylsertraline > fluoxetine ≥ sertraline > mirtazapine > > > venlafaxine (Richelson, 1997). Several in vivo studies have shown no significant effect of paroxetine, sertaline, or fluoxetine on prototypical CYP3A4 substrates. Grapefruit juice, ketoconazole, itraconazole, diltiazem, and verapamil are also CYP3A4 inhibitors.

CYP1A2. About 12% of the population are "slow metabolizers" of CYP1A2. However, it may be that this difference is the result of enzyme induction rather than genetic polymorphism. CYP1A2 activity is increased by cigarette smoke, charcoal-grilled foods, and cabbage, which can markedly alter the pharmacokinetics of CYP1A2 substrates. Thus, "slow metabolizers" may not have been environmentally induced to the same extent as their more "rapid-metabolizing" counterparts (Eaton et al., 1995).

Substrates of CYP1A2 include acetominophen, caffeine, clozapine, haloperidol, propranolol, phenothiazines, phenacetin, tertiary TCAs, theophylline, tetrahydroacridinamine (Tacrine), and warfarin.

Of the antidepressants studied, fluvoxamine is clearly the most potent inhibitor of CYP1A2. It profoundly decreases the clearance of several drugs, including certain benzodiazepines, theophylline, and warfarin (Medical Economics, 1997c). Warnings have been issued concerning its concomitant use with these drugs. In particular, fluvoxamine should not ordinarily be coadministered with diazepam. When coadministered with fluvoxamine, alprazolam dosage should be reduced by 50% and theophylline by 33%. Moreover, warfarin levels, together with prothrombin times, should be monitored closely.

The relative potency of inhibition of CYP1A2 among antidepressants is: fluvoxamine > > > paroxetine = sertraline > fluoxetine = norfluoxetine = nefazodone > mirtazapine > > > venlafaxine (Richelson, 1997). There is no evidence that antidepressants other than fluvoxamine cause clinically meaningful inhibition of this isoenzyme. Grapefruit juice, floroquinolones, and tertiary tricyclic antidepressants are also CYP1A2 inhibitors.

CYP2C. CYP2C is a subfamily of enzymes that includes 2C9, 2C10, 2C19, and others. CYP2C19 is known to exhibit genetic polymorphism, with approximately 18% of Japanese, 19% of African Americans, 8% of Africans, and 3–5% of Caucasians reported to be poor metabolizers of the prototype CYP2C substrate mephenytoin.

CYP2C substrates include diazepam, citalopram, TCAs, warfarin, phenytoin, omeprazole, tolbutamide, some nonsteroidal antiinflammatory agents, hexobarbital, and others.

Fluvoxamine carries a warning about being prescribed with warfarin (Medical Economics, 1997c). Other information on the inhibitory effects of antidepressants on CYP2C is limited. However, fluvoxamine and fluoxetine are considered more potent inhibitors than paroxetine, fluoxetine, and sertraline (Ereshefsky, 1996). Venlafaxine and nefazodone are weak inhibitors of CYP2C.

VELAFAXINE

Most of the data on the effects of venlafaxine on the cytochrome P_{450} system has been derived from studies using the immediate release (IR) formulation, which is dosed two or three times daily. An extended release (XR) formulation of venlafaxine has recently been introduced to the market which allows the drug to be dosed once daily. While the XR may have certain advantages in terms of compliance and side effect profile, the effects of the XR formulation on the cytochrome P_{450} system are less clear. The XR formulation releases venlafaxine much more slowly into the gastrointestinal tract than the IR formulation. Consequently, time to peak plasma concentrations are increased (T_{max} = 5.5 h for the XR formulation compared to 2 h for the IR formulation), and peak plasma concentration is lower (C_{max} = 150 ng/ml for the XR formulation compared to 225 ng/ml for the IR formulation) (Wyeth-Ayerst Laboratories, Inc., 1997). A lower C_{max} may actually lessen venlafaxine's potential for P_{450} interactions. A lower Cmax may correspond with lower hepatic concentrations, and decrease the competitive inhibition of venlafaxine on the cytochrome system.

Notably, C_{max} and T_{max} are the only pharmacokinetic parameters reported to be different between the XR and IR formulations (Wyeth-Ayerst Laboratories, Inc.). AUC is similar for both formulations. Elimination half-life ($t_{1/2}$), volume of distribution, and protein binding are not changed. Because their pharmacokinetic profiles are similar, the XR and IR formulations are likely to exert similar effects on the cytochrome P_{450} system. Clearly, however, more research is necessary in this area.

CYP2D6. Over 55% of a single oral dose of venlafaxine IR is excreted in the urine as O-desmethylvenlafaxine (ODV) or ODV-glucuronide (Howell et al., 1993). The metabolism of venlafaxine to ODV is quite different in extensive metabolizers (EM) compared to poor metabolizers (PM), but this has uncertain clinical consequences, because venlafaxine and ODV are pharmacologically similar. The total concentration of active moiety (venlafaxine plus ODV) is similar in EM and PM (Otton et al., 1996), and therefore no dosage adjustment appears necessary in PM or when venlafaxine is coadministered with CYP2D6 inhibitors (Wyeth-Ayerst Laboratories, Inc., 1997).

Venlafaxine is administered as a racemic mixture of R(+) and S(–) enantiomers, both of which exhibit pharmacologic activity (Otton et al., 1996). The K_i for CYP2D6 for racemic, S(–), and R(+) venlafaxine are 33 μM, 22 μM, and 52 μM, respectively. These values are approximately 1–3 orders of magnitude greater (less potent) than paroxetine (K_i = 0.07 μM), fluoxetine (K_i = 0.15 μM), norfluoxetine (K_i = 0.19 μM), sertraline (K_i = 1.2 μM), and fluvoxamine (K_i = 1.8 μM). At recommended doses of 75–375 mg daily, steady-state plasma concentrations of venlafaxine are considerably lower than the K_i for CYP2D6. This relatively low affinity suggests that in vivo inhibition of CYP2D6 by venlafaxine is less likely than SSRI antidepressants.

In vivo data has largely but not totally confirmed these in vitro results. Dextromethorphan (DM) to dextrophan (DT) ratios were evaluated in normal subjects treated with fluoxetine (20 mg daily for 28 days) or venlafaxine (37.5 mg twice daily for 7 days, then 75 mg twice daily for 21 days) (Amchin et al., 1997a). DM/DT ratios were significantly higher in the fluoxetine group on days 7, 28, and 42, suggesting that fluoxetine is a more potent inhibitor of CYP2D6 than venlafaxine. In another study comparing the effects of paroxetine, sertraline, fluoxetine, and venlafaxine on DM/DT ratios, paroxetine and fluoxetine were found to be significant inhibitors of CYP2D6, with 83% and 42% of subjects converted to PMs, respectively (Lam et al., 1997). Neither sertraline nor venlafaxine significantly inhibited CYP2D6 activity in this study, though the former agent has been shown to do so in other studies.

Risperidone is completely metabolized by CYP2D6. When coadministered with venlafaxine (150 mg/day) under steady-state conditions, risperidone conversion to its active metabolite, 9-OH-risperidone, after a 1 mg dose was slightly inhibited, resulting in a modest 32% increase in its AUC (Amchin et al., 1997b). However, the pharmacokinetic profile of the total active moiety (risperidone plus 8-OH-risperidone) was not altered and therefore is unlikely to be clinically significant.

Haloperidol is metabolized in part by CYP2D6. Venlafaxine (150 mg/day) administered under steady-state conditions decreased total oral-dose clearance of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in heloperidol AUC (Wyeth-Ayerst Laboratories, Inc., 1997). In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the elimination $t_{1/2}$ was unchanged. The mechanism of this interaction is unknown and may not be due solely to an effect on CYP2D6, or even to an interaction involving the P450 system. Nonetheless, dosing adjustments of haloperidol may be necessary when coadministering these two medications.

Imipramine is 2-hydroxylated by CYP2D6. In a

comparative study of venlafaxine and SSRIs using human liver microsomal incubations, venlafaxine was a 1.5- to 26-fold less potent inhibitor than the SSRIs (Ball et al., 1997). The K_i values of fluoxetine, paroxetine, fluvoxamine, and sertraline were 1.6, 3.2, 8.0, and 24.7 μM, respectively. The K_i for venlafaxine was 41.0 μM. Notably, both imipramine and desipramine markedly inhibited venlafaxine metabolism to ODV, but this inhibition was not thought to be clinically significant due to the similar pharmacological profile of venlafaxine and ODV.

Velafaxine does not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, the active metabolite of imipramine was affected (Wyeth-Ayerst Laboratories, Inc., 1997). Thus, desipramine AUC, C_{max}, and C_{min} increased 35% in the presence of venlafaxine. Similarly, 2-OH-desipramine AUC increased 2.5- to 4.5-fold, depending on the dose of venlafaxine administered. Therefore, imipramine and desipramine should be administered with caution with venlafaxine.

These studies taken together suggest that even though venlafaxine is in general a less potent inhibitor of CYP2D6 than the SSRIs, caution should be exercised when administering venlafaxine with CYP2D6 substrates, particularly in those with a low therapeutic index.

CYP3A4. In poor metabolizers of CYP2D6, CYP3A4 is a likely alternative metabolic pathyway. CYP3A4 N-demethylates venlafaxine to an inactive metabolite. Venlafaxine does not inhibit CYP3A4 activity (Wyeth-Ayerst Laboratories, Inc., 1997). When using testosterone 6 β-hydroxylase activity as a marker of CYP3A4, venlafaxine showed no inhibition at concentrations of up to 1 μM (Ball et al., 1997).

In vivo studies generally but not always confirm in vitro results. In a recent review of venlafaxine (Ereshevsky, 1996), Ereshevsky reports the results of a European in vivo study which demonstrated that venlafaxine did not significantly alter the plasma concentration of carbamazepine or its metabolites.

In an open label study using the prototypic CYP3A4 substrate, terfenadine (single 120 mg dose), subjects who received venlafaxine at steady-state conditions (75 mg twice daily) did not exhibit altered terfenadine pharmacokinetics (Amchin et al., 1997d). Plasma concentrations of the terfenadine acid metabolite were slightly decreased in the presence of venlafaxine, but this effect was not thought to be mediated by effects on the P_{450} system.

Alprazolam pharmacokinetics have been reported to be only slightly changed in the presence of venlafaxine. In vitro, venlafaxine, NDV, and ODV produced less than a 10% change in the rate of metabolism of alprazolam to 4-OH-alprazolam at 250 μM, which far exceeds levels encountered in clinical usage (von Moltke et al., 1997). In contrast, fluvoxamine produces a marked, dose-dependent inhibition of alprazolam metabolism. In vivo, when a single 2 mg dose of alprazolam was given to normal subjects treated with venlafaxine (75 mg twice daily) at steady-state conditions, alprazolam clearance increased 35%, resulting in a 28% decrease in AUC (Amchin and Zarycranski, 1996). A preliminary review indicated that these pharmacokinetic changes were not associated with clinically meaningful effects.

Venlafaxine had similar effects on diazepam metabolism. When subjects pretreated with multiple dose venlafaxine (150 mg in divided doses) or placebo received a single 5 mg dose of diazepam, the antidepressant increased diazepam clearance and volume of distribution and decreased diazepam AUC (Troy et al., 1995). Critical flicker fusion scores were also reported as altered, though reanalysis of the data revealed that immediate word recall scores were altered instead. This may be clinically significant in that immediate word recall was the only pharmacodynamic variable not averaged over 8 h after administration. Rather, immediate word recall scores were evaluated only during the first h following diazepam administration, when maximal interactions between diazepam and venlafaxine occur. Other pharmacodynamic variables were averaged for the 8 h post-administration and may be less sensitive indicators of a diazepam–venlafaxine interaction. Moreover, single dose studies may not properly account for distributions kinetics and the effects of active metabolites. Therefore, these results are difficult to interpret. It is, however, noteworthy that venlafaxine had similar effects on alprazolam and diazepam disposition, decreasing the AUC of both significantly. The mechanism and clinical significance of this finding is unclear. Further research into venlafaxine–benzodiazepine interactions is warranted.

Other CYP. Ball et al. (1997) reported that venlafaxine did not inhibit CYP1A2 or CYP2C9 activity, even at concentrations of 1 mM. Another in vitro study confirmed the lack of effect of venlafaxine on CYP1A2 activity even at concentrations as high as 400–500 μM (von Moltke et al., 1996). In vivo, venlafaxine did not significantly alter the pharmacokinetic profile of caffeine, a CYP1A2 substrate (Amchin et al., 1997c).

Cimetidine is a nonselective P450 inhibitor. Not surprisingly, venlafaxine clearance is decreased 43% by coadministration of cimetidine (Ereshefsky, 1996), and venlafaxine AUC and C_{max} are increased approximately 60%. This decreased clearance is likely secondary to the inhibition of first pass metabolism of venlafaxine by cimetidine. No effect on ODV metabolism was noted. Thus, the net effect of these pharmacokinetic alterations is pharmacodynamically slight at best in terms of venlafaxine effects. No dosage adjustments were recommended from these findings. However, the effects may be more pronounced in patients with hepatic dysfunction or in the elderly. In such at-risk populations, caution concerning potential drug–drug interactions is advised.

NEFAZODONE

Nefazodone, a potent $5HT_{2A}$ antagonist that also inhibits both serotonin and norepinephrine reuptake, is extensively metabolized in liver. Less than 1% is excreted unchanged in urine. OH-NEF is the major metabolite and has equivalent activity to nefazodone at 5-HT_{2A} receptors and 5HT reuptake sites. A triazoledione metabolite has weak $5HT_{2A}$ activity. Metachlorophenylpiperazine (mCPP) is a minor metabolite and displays similar activity to the parent compound at serotonin reuptake sites but has little affinity for the $5HT_{2A}$ receptors (Davis et al., 1997).

CYP2D6. In vitro analysis with human liver microsomes demonstrates that nefazodone and its metabolites are weak inhibitors of CYP2D6, with an average K_i ranging from 18–50 μM for dextrophan formation (Schmider et al., 1996). These K_i values are at least 100-fold higher (less potent) than fluoxetine (K_i = 0.1 μM). Moreover, nefazodone and OH-NEF steady-state kinetics are not significantly different in poor as compared to extensive metabolizers of CYP2D6 (Barbhaiya et al., 1996a). However, C_{max} and AUC values for mCPP are twofold and fourfold higher, respectively, in the PM subjects compared to EM subjects, indicating that the metabolism of mCPP is dependent on CYP2D6. The increased mCPP plasma levels in PM subjects, however, do not seem to influence the disposition or safety profile of nefazodone in PM subjects.

In vivo drug interaction studies generally confirm in vitro results. Once steady-state levels of nefazodone are attained, it exerts a weak inhibitory effect on haloperidol metabolism (5 mg dose) in extensive metabolizers (Barbhaiya et al., 1996b). There was a 36% increase in AUC for haloperidol, as well as nonsignificant increases in haloperidol's C_{max} and C_{12h}. Of note, there were some psychomotor performance differences noted in the treatment groups, but these effects were not consistently and clearly demonstrated, and had uncertain clinical significance. Nefazodone metabolism was not affected. Based on these results, dosage adjust may be necessary when the two medications are administered together. Importantly, there were no poor metabolizers of CYP2D6 included in this study.

Nefazodone has a modest effect on propranolol metabolism (Salazar et al., 1995b). In healthy males, the T_{max} for propranolol increased from day 5 to day 6, and the C_{max} and AUC of both propranolol and OH-propranolol were lower. No consistent alterations in the pharmacological effects of propranolol were found. Although the pharmacokinetics of nefazodone itself were not affected, the C_{max}, AUC, and C_{min} of mCPP were significantly increased, as was the mCPP/NEF ratio, especially in poor metabolizers of CYP2D6. These results likely have minimal clinical significance, but it is important to note that such interactions may be very relevant in treating older patients with known heart disease. It is also notable that there was one noncompleter in this study who dropped out after developing syncope and orthostasis after day 6 of combined nefazodone/propranolol treatment.

CYP3A4. Unlike CYP2D6, there is no gold standard substrate such as dextromethorphan for CYP2D6 to measure and standardize CYP3A4 activity. Consequently, nefazodone-induced inhibition of CYP3A4 activity has been primarily demonstrated in vivo. Nefazodone has been demonstrated to be a potent CYP3A4 inhibitor in several clinical studies in which the metabolism of known CYP3A4 substrates were measured in subjects treated with nefazodone.

When a single 0.25 mg dose of triazolam was administered to healthy men treated with nefazadone (200 mg twice daily for 7 days), triazolam pharmacokinetics were significantly altered (Barbhaiya et al., 1995b; Kroboth et al., 1995). The triazolam C_{max} and AUC were increased in the presence of nefazodone 1.7- and 4-fold, respectively, and the mean plasma concentration was 60% higher. In addition, there was a corresponding significant 2.5- to 8-fold increase in psychomotor impairment when triazolam and nefazodone were coadministered. Thus, when triazolam and nefazodone are coprescribed, triazolam doses should be reduced by 75% (Medical Economics, 1997a).

Similar results were obtained with alprazolam (Greene et al., 1995a; Kroboth et al., 1995). When alprazolam (1 mg twice daily) is coadministered with nefazodone (200 mg twice daily for 7 days), the C_{max} and AUC of alprazolam increased twofold; for alprazolam's metabolite, 4-OH-alprazolam, there was a 40% and 26% increase in C_{max} and AUC, respectively. In addition, alprazolam $t_{½}$ increased from 10.8 h to 22.1 h when coadministered with nefazodone. Consequently, alprazolam did not attain steady-state concentrations until day 5, as compared to day 3 when alprazolam was administered alone. Notably, the pharmacokinetics of nefazodone and OH-NEF were not changed, but mCPP C_{max} and AUC increased 2.5-fold. These effects were not seen after day 1 of treatment, but were seen after 7 days of treatment. Nefazodone and alprazolam coadministration also increased psychomotor impairment and sedation. When administered with nefazodone, alprazolam dose should be reduced by 50% (Medical Economics, 1997a).

Lorazepam, which is not primarily metabolized by oxidative processes in the liver, undergoes 75% glucuronidation. When coadministered with nefazodone, there are no pharmacokinetic alterations in either lorazepam or nefazodone metabolism (Greene et al., 1995b; Kroboth et al., 1995). Surprisingly, there was a decrease in the C_{max} and AUC of mCPP by 36% and 39%, respectively, by a mechanism which remains obscure. This effect is probably not clinically significant, and therefore no dose adjustment is necessary when lorazepam and nefazodone are administered together.

It should be noted that other medications which in-

hibit CYP3A4, such as ketoconazole and erythromycin, elevate plasma concentrations of terfenadine and astemizole, which may be associated with fatal cardiac arrthymias. The effect of nefazodone on these antihistamines is unknown. However, its use is contraindicated with these two antihistamines, as well as cisapride, due to their putative, potentially fatal interaction (Medical Economics, 1997b).

An interaction between nefazodone and carbamazepine has also been described (Ashton and Wolin, 1996). After initiation of nefazodone, carbamazepine plasma concentrations increased in a patient with epilepsy, resulting in carbamazepine toxicity. Close monitoring of carbamazepine levels is, of course, always recommended.

CYP2C. The lack of interaction between nefazodone and CYP2C substrates suggests that it is a weak inhibitor of this isoenzyme. There was no significant effect on the AUC, C_{max}, t_{max}, or $t_{1/2}$ of a single 300 mg dose of phenytoin when administered to healthy male subjects receiving nefazodone (200 mg twice daily) at steady-state levels (Marino et al., 1997). There were no demonstrable pharmacodynamic alterations either. Although these results do not preclude the possibility of an interaction between nefazodone and phenytoin when phenytoin is administered on a long-term basis, such an interaction is thought to be unlikely, and no dosage adjustment of phenytoin is recommended when coadministered with nefazodone.

Warfarin is known to interact with several antidepressants, several of which lead to increased prothrombin or bleeding times (Salazar, 1995a), though no such results were obtained with nefazodone. Nefazodone had no significant effect on the unbound fraction of total warfarin in plasma or on the steady-state pharmacokinetics of R-warfarin. There was a significant 12% decrease in the steady-state AUC and C_{max} of S-warfarin, which may be clinically significant because S-warfarin contributes most of the therapeutic effects of warfarin. However, no serious or unexpected adverse events suggestive of abnormal bleeding occurred in the healthy volunteers, and the prothrombin ratio and bleeding times remained unchanged.

CYP1A2. In vitro, nefazodone is a weak inhibitor of CYP1A2. Using the O-deethylation of phenacetin to acetaminophen a measure of CYP1A2 activity, nefazodone (K_i = 65 μM) was a tenfold-less potent inhibitor than fluoxetine (K_i = 4.4 μM), sertraline (K_i = 8.8 μM), and paroxetine (K_i = 5.5 μM), and far less potent than fluvoxamine (K_i = 0.24 μM) (von Moltke et al., 1996).

Theophylline is metabolized by CYP1A2, CYP2E1, and, to a lesser extent, CYP2D6 (Dockens et al., 1995). The effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline was evaluated in 13 patients with chronic obstructive pulmonary disease treated with theophylline therapy. When nefazodone (200 mg twice daily) and theophylline (600–1,200 mg daily) were coadministered for 7 days, nefazadone did not affect the pharmacokinetics or pharmacodynamics of theophylline, as determined by measurement of plasma levels, AUC, C_{min}, C_{max}, and FEV_1. Thus, no dose adjustment in theophylline is necessary when coadministered with nefazodone.

Other CYP. Cimetidine is a nonspecific P450 inhibitor which has been shown to interact with many medications in a somewhat variable manner, but it seems to exert minimal effects on the metabolism of nefazodone. The coadministration of nefazodone and cimetidine for 1 week showed no change in steady-state pharmacokinetic parameters for cimetidine, nefazodone, or OH-nefazodone (Barbhaiya et al., 1995a). Steady-state mCPP C_{max} and AUC values were 37% higher, but this is probably not clinically significant.

Digoxin commonly interacts with a number of other medications resulting in clinically significant effects because of the narrow therapeutic index of this drug. Similarly, digoxin also has a significant interaction with nefazodone. When nefazodone (200 mg twice daily) and digoxin (0.2 mg daily) were coadministered for 8 days, digoxin AUC, C_{min}, C_{max} were increased 15%, 27%, and 29% respectively (Dockens et al., 1996). The C_{min} in particular may be of clinical significance. No EKG changes were observed in healthy subjects, but this measure may be a relatively insensitive marker for detecting toxicity. Therefore, when digoxin and nefazadone are coadministered, digoxin levels should be closely monitored.

MIRTAZAPINE

There is relatively little data available on the effects of mirtazapine on the cytochrome P450 system and its potential to interact with other drugs in vivo. Such research is clearly needed. Preclinical research has revealed that mirtazapine has three metabolites: 8-hydroxylation occurs by an action of CYP2D6 and to a lesser extent CYP1A2; N(2)-demethylation by CYP1A2 and CYP3A4; and N(2)-oxidation by CYP3A4 (Dahl et al., 1997).

To determine the effects which CYP2D6 polymorphism exerts on mirtazapine pharmacokinetics, a single 15 mg oral dose of mirtazapine was given to 7 EM and 7 PM subjects, and plasma concentrations of mirtazapine and its demethyl metabolite were monitored over 3 days (Dahl et al., 1997). No significant differences were seen in T_{max}, C_{max}, AUC, clearance, $t_{1/2}$ or volume of distribution between EM and PM subjects. Thus, its disposition is independent of polymorphic CYP2D6 activity.

In vitro, mirtazapine is a weak inhibitor of each of these isoenzymes (Dahl et al., 1997). For CYP2D6, mirtazapine (K_i = 41 μM) is a tenfold-less potent inhibitor than fluoxetine (K_i = 4 μM). For CYP1A2, mirtazapine (K_i = 159 μM) is a far less potent inhibitor than fluvoxamine (K_i = 0.18 μM) by a factor of three orders of magnitude. For CYP3A4, mirtazapine (K_i =

210 μM) is also a very weak inhibitor compared to ketoconazole (K_i = 0.07 μM).

The calculated in vivo inhibition using the formula $[I/(K_i + I)]*100\%$, for a mirtazapine dose of 15 to 45 mg and an estimated hepatic concentration of 0.4–1.2 μM, is 0.75% at CYP1A2, 2.8% at CYP2D6, and 0.57% at CYP3A (Delbressine and Vos, 1997). These results indicate that mirtazapine has a very low potential for clinically relevant interactions with other drugs. At the present time, results from in vivo studies are not yet available.

DISCUSSION

Physicians should be cognizant of potential drug–drug interactions during treatment with antidepressants. There is the potential for drug interactions between any agent metabolized by a P_{450} enzyme and another drug that inhibits that enzyme. CYP2D6 has received the most attention. However, other isozymes, particularly CYP3A4, may ultimately prove more important in the mediation of clinically important drug interactions. Substrates with a narrow therapeutic window, such as TCAs, theophylline, phenytoin, tolbutamide, carbamazepine, terfenadine, astemizole, type 1C antiarrhythmics, or antipsychotics, should be administered with caution during therapy with any antidepressant known or suspected to inhibit the metabolism of that drug.

Venlafaxine, nefazodone, and mirtazapine have cytochrome P_{450} inhibitory profiles which are different from each other and the SSRIs. As a class, the SSRIs are more potent CYP2D6 and CYP1A2 inhibitors than venlafaxine, nefazodone, and mirtazapine. As a class, they are also more potent CYP3A4 inhibitors than venlafaxine and mirtazapine as well, but less potent than nefazodone.

In summary, venlafaxine has been shown to lack any significant effects on CYP1A2, CYP3A4, and CYP2C activity in vitro. The CYP3A4 results have been confirmed in vivo. Carbamazepine and terfenadine pharmacokinetics were unchanged when coadministered with venlafaxine, while alprazolam and diazepam showed an unexpectedly decreased AUC, which was of questionable clinical significance. Studies on single dose benzodiazepines may not properly account for distribution kinetics nor accurately reflect steady-state conditions. Moreover, the investigators in the diazepam study interpreted the pharmacodynamic results in a somewhat unusual way. Further studies on the effect of venlafaxine on benzodiazepines are warranted. Venlafaxine is a weak CYP2D6 inhibitor. When coadministered with venlafaxine, imipramine pharmacokinetics were unchanged, but risperidone and haloperidol AUC increased significantly, as did desipramine AUC, C_{max} and C_{min}, and 2-OH-despramine AUC. These results indicate that dosage adjustments of CYP2D6 substrates may be necessary when administered with venlafaxine.

Nefazodone is a potent CYP3A4 inhibitor and is contraindicated with terfenadine, astemizole, and cisapride. A potential interaction between nefazodone and carbamazepine has also been described. When coadministered with nefazodone, triazolam and alprazolam dosages should be decreased 75% and 50%, respectively. No dosage adjustment is necessary with lorazepam, which is not metabolized by CYP3A4. Nefazodone is a weak CYP2D6 inhibitor, showing no clinically significant interaction with haloperidol or propranolol. However, in the study with propranolol, one patient developed acute orthostatic hypotension and syncope on day 6 of combined treatment and could not continue with the study. His symptoms may or may not have been the result of coadministration of propranolol with nefazodone. Nefazodone is a weak CYP2C inhibitor as well. Single-dose theophylline pharmacokinetics were not altered by nefazodone, and S-warfarin AUC and C_{max} increased 12%, but did not change the prothrombin ratio or bleeding times of healthy volunteers. Nefazodone is a tenfold-less potent inhibitor of CYP1A2 than fluoxetine, sertraline, and paroxetine.

Mirtazapine shows much less in vitro inhibition at CYP2D6, CYP1A2, and CYP3A4 than fluoxetine, fluvoxamine, and ketoconazole, respectively. However, in vivo studies are lacking. Although it is unlikely that mirtazapine is involved in significant drug–drug interactions, such studies would be welcome.

These results demonstrate that the antidepressants most recently introduced have different profiles of cytochrome P_{450} inhibition when compared to previous antidepressants studied. However, it must be appreciated that many of these studies are tightly controlled and somewhat limited in scope. Results may therefore vary in more diverse populations and conditions. Nonetheless, as more becomes known about these drugs and others, clinicians will have greater flexibility in treating depression and comorbid illnesses effectively while minimizing potentially dangerous and harmful side effects.

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REFERENCES

Amchin J, Ereshefsky L, Zarycranski WM (1997a) Effect of venlafaxine versus fluoxetine on the metabolism of dextromethorphan, a CYP2D6 marker. Presented at the 149th Annual Meeting of the American Psychiatric Association, San Diego, CA; May 1997.

Amchin JD, Zarycranski W (1996) Effect of venlafaxine on the pharmacokinetics of alprazolam. Psychopharmacol Bull 32:410.

Amchin JD, Zarycranski W, Taylor K (1997b) Effect of venlafaxine on the pharmacokinetics of risperidone. Presented at the 37th Annual New Clinical Drug Evaluation Unit Program, Boca Raton, Florida; May 1997.

Amchin J, Zarycranski W, Taylor K. (1997c) Evidence that venlafaxine does not inhibit CYP1A2 as measured in vivo by the metabolism of caffeine. Presented at the 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, CA; March 5–8, 1997.

Amchin JD, Zarycranski W, Taylor K (1997d) Venlafaxine's lack of CYP3A4 inhibition is further confirmed by an in vivo study with terfenadine. Presented at the 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, CA; March 5–8, 1997.

Ashton AK, Wolin RE (1996) Nefazodone-induced carbamazepine toxicity [letter]. Am J Psychiatry 153:733.

Ball SE, Ahern D, Scantina J, Kao J (1997) Venlafaxine: In vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRI's, and effects on human hepatic CYP3A4, CYP2C9, and CYP1A2. Br J Clin Pharmacol 43:619–626.

Barbhaiya RH, Buck AB, Greene DS (1996a) Single and multiple dose pharmacokinetics of nefazodone in subjects classified as extensive and poor metabolizers of dextromethorphan. Br J Clin Pharmacol 42:573–581.

Barbhaiya RH, Shukla UA, Greene DS (1995a) Lack of interaction between nefazodone and cimetidine: A steady-state pharmacokinetic study in humans. Br J Clin Pharmacol 40:161–165.

Barbhaiya RH, Shukla UA, Greene D, Brenel HP, Midha KK (1996b) Investigation of pharmacokinetic and pharmacodynamic interaction after coadministration of nefazodone and haloperidol. J Clin Psychopharmacol 16:26–34.

Barbhaiya RH, Shukla UA, Kroboth PD, Greene DS (1995b) Coadministration of nefazodone and benzodiazepine: II. A pharmacokinetic interaction study with triazolam. J Clin Psychopharmacol 15:320–326.

Dahl ML, Voortman G, Alm C, Elwin CE, Delbressine L, Vos R, Bogarrds JJP, Bertilsson L (1997) In vitro and in vivo studies on the disposition of mirtazapine in humans. Clin Drug Invest 13:37–46.

Davis R, Whittington R, Bryson HM (1997) Nefazodone: A review of its pharmacology and clinical efficiency in the management of major depression. Drugs 53:608–636.

Delbressine LPC, Vos RME (1997) The clinical relevance of preclinical data: Mirtazapine, a model compound. J Clin Psychopharmacol 17(suppl 1):29S–33S.

Dockens RC, Greene DS, Barbhaiya RH (1996) Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. J Clin Pharmacol 36:160–167.

Dockens RC, Rapoport D, Roberts D, Greene DS, Barbhaiya RH (1995) Lack of an effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline during concurrent administration in patients with chronic obstructive pulmonary disease. Br J Clin Pharmacol 40:598–601.

Eaton DL, Gallagher EP, Bammler TK, Kunze KL (1995) Role of cytochrome P4501A2 in chemical carcinogenesis: Implications for human variability in expression and enzyme activity. Pharmcogenetics 5:259–274.

Eichelbaum M, Gross AS (1990) The genetic polymorphism of debrisoquine/sparteine metabolism: Clinical aspects. Pharmacol Ther 46:377–394.

Ereshefsky L (1996) Drug–drug interactions involving antidepressants: Focus on venlafaxine. J Clin Psychopharmacol 16(suppl 2):37S–50S.

Ereshefsky L, Overman GP, Karp JK (1996) The 1996 Black Book of Psychotropic Dosing and Monitoring. New York: MBL Communications, pp 14–15.

Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH (1995a) Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. J Clin Psychopharmacol 15:399–408.

Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH (1995b) Coadministration of nefazodone and benzodiazepines: IV. A pharmacokinetic interaction study with lorazepam. J Clin Psychopharmacol 15:409–416.

Howell SR Husbands GEM, Scantina JA, Sisenwine SF (1993) Metabolic disposition of 14C-venlafaxine in mouse, rat, dog, rhesus moneky, and man. Xenobiotica 23:349–359.

Kroboth PD, Folan MM, Lush RM, Chaikin PC, Shukla UA, Barbhaiya R, Salazar DE (1995) Coadministration of nefazodone and benzodiazepines: I. Pharmacodynamic assessment. J Clin Pharmacol 15:306–319.

Kroemer HK, Eichelbaum M. (1995) "It's the genes, stupid": Molecular basis and clinical consequences of genetic cytochrome P450 2D6 polymorphism. Life Sci 56:2285–2298.

Lam YWF, Alfaro C, Ereshevsky L, Amchin J (1997) Cross-over comparison of CYP2D6 inhibition: Insignificant effect of venlafaxine compared to sertraline, paroxetine, and fluoxetine. Presented at the 150th Annual Meeting of the American Psychiatric Association, San Diego, CA; May 1997.

Marino MR, Langenbacher KM, Hammett JL, Nichola P, Uderman HD (1997) The effect of nefazodone on the single-dose pharmacokinetics of phenytoin in healthy male subjects. J Clin Psychopharmacol 17:28–33.

Medical Economics (1997a) Physician's Desk Reference, 51st ed. Montvale, NJ: Medical Economics, pp 776–779 (nefazodone).

Medical Economics (1997b) Physician's Desk Reference, 51st ed. Montvale, NJ: Medical Economics, pp. 935–940 (fluoxetine).

Medical Economics (1997c) Physician's Desk Reference, 51st ed. Montvale, NJ: Medical Economics, pp 2723–2727 (fluvoxamine).

Nemeroff CB, DeVane CL, Pollock BG (1996) Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 153:311–320.

Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, Sellers EM (1996) Venlafaxine oxidation in vitro is catalyzed by CYP2D6. Br J Clin Pharmacol 41:149–156.

Richelson E (1997) Pharmacokinetic drug interactions of new antidepressants: A review of the effects on the metabolism of other drugs. Mayo Clin Proc 72:835–847.

Salazar DE, Dockens RC, Milbrath RL, Raymond RH, Fulmor E, Chaikin PC, Uderman HD (1995) Pharmacokinetic and pharmacodynamic evaluation of warfarin and nefazodone coadministration in healthy subjects. J Clin Pharmacol 35:730–738.

Salazar DE, Marathe PH, Fulmor IE, Lee JS, Raymond RH, Uderman HD (1995) Pharmacokinetic and pharmacodynamic evaluation during coadministration of nefazodone and propranolol in healthy men. J Clin Pharmacol 35:1109–1118.

Schmider J, Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI (1996) Inhibition of cytochrome P450 by nefazodone in vitro: Studies of dextromethorphan O- and N-demethylation. Br J Clin Pharmacol 41:339–343.

Troy SM, Lucki I, Peirgies AA, Parker VD, Klockowski PM, Chiang ST (1995) Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and diazepam. J Clin Pharmacol 35:410–419.

von Moltke LL, Duam SX, Greenblatt DJ, Fogelman SM, Schmider J, Harmatz JS, Shader RI (1997) Venlafaxine and metabolites are weak inhibitiors of human cytochrome P450-3A isoforms. Biol Psychiatry 41:377–380.

von Moltke LL, Greenblatt DJ, Duam SX, Schmider J, Kudchadker L, Fogelman SM, Harmatz JS, Shader RI (1996) Phenacetin O-deethylation by human liver microsomes in vitro: Inhibition by chemical probes, SSRI antidepressants, nefazodone, and venlafaxine. Psychopharmacology 128:398–407.

Wyeth-Ayerst Laboratories, Inc. (1997) Effexor XR (venlafaxine hydrochloride)(package insert). Philadelphia, PA: Wyeth-Ayerst Laboratories, Inc.