Pharmacokinetic Interactions of Antidepressants

Elliott Richelson, M.D.

Seven of the newest antidepressants are the serotonin selective reuptake inhibitors (fluoxetine, sertraline, paroxetine, and fluvoxamine [currently approved in the United States for obsessive-compulsive disorder only]), a serotonin norepinephrine reuptake inhibitor (venlafaxine), a postsynaptic serotonin antagonist/presynaptic serotonin reuptake inhibitor (nefazodone), and presynaptic/postsynaptic noradrenergic/serotonergic receptor antagonist (mirtazapine). Many of these drugs are potent inhibitors of the cytochrome P450 (CYP) enzymes of the liver. The CYP enzymes most relevant to the use of antidepressants and for which the most thorough data are available are the CYP1A2, CYP2D6, and CYP3A4. These 3 CYP isoenzymes are discussed in relation to some of the drugs they metabolize, and appropriate cautions are recommended for concurrent administration of these new antidepressants and other drugs frequently prescribed to elderly patients. *(J Clin Psychiatry 1998;59[suppl 10]:22–26)*

The pharmacokinetic drug interactions of antidepressants is a very complex topic. To assist in clarifying these interactions, an introductory primer on clinical pharmacology follows later in this article. However, 3 main points are key to understanding drug interactions. First, pharmacokinetic drug interactions are a *potential* and not a *certain* problem. Second, these interactions are more likely to occur with what we call high-risk drugs: fluvoxamine at cytochrome P450 1A2 (CYP1A2), fluoxetine and paroxetine at CYP2D6, and nefazodone at CYP3A4. Third, interactions are unlikely to occur with what are called low-risk drugs, namely, sertraline, venlafaxine, and probably bupropion and mirtazapine, but they can occur. A more in-depth discussion of this topic can be found in recent reviews.[1–3]

DRUG INTERACTIONS

Pharmacodynamic Drug Interactions

In general, there are 2 kinds of drug interactions that are especially pertinent to antidepressants. One is pharmacodynamic, the second is pharmacokinetic. The first asks the question: Does the antidepressant drug affect the mechanism of action of another drug that the patient may be taking? That is, does drug A affect the mechanism of action of drug B? An example of this type of interaction would be if a patient were taking a tricyclic antidepressant that blocks the reuptake of norepinephrine and the patient gets a cold. He or she would go to the pharmacy and get an over-the-counter cold remedy that contains as an ingredient a sympathomimetic drug. The action of that drug can be prolonged as a result of its not being taken into the nerve ending, where it is partly inactivated.

Pharmacokinetic Drug Interactions

The main focus of this article is pharmacokinetic drug interactions. This type of interaction poses the question: Does the antidepressant drug affect the metabolism of another drug that the patient may be taking? An example of a pharmacokinetic drug interaction deals with the analgesic, opioid drug codeine (methylmorphine), which is not very potent at the opiate receptor. To cause its pharmacologic effects, it needs to be converted to morphine. This transformation is achieved by the action of the liver enzyme CYP2D6. Let us now suppose that the patient is taking fluoxetine, a drug that potently inhibits this particular enzyme. As a result, the patient would need a much higher dose of codeine than normally required in order to achieve the desired clinical effect.

Costs of Drug Interactions

The overall topic of this supplement is late-life depression. Of course, pharmacokinetic as well as pharmacodynamic drug interactions can be especially problematic in the elderly patient, who is likely to be taking multiple medications. Such interactions, whether they are pharmacodynamic or pharmacokinetic, can lead to measurable clinical costs. These costs accrue from poorer outcomes that are due to increased adverse effects. In addition, depending on the drug combination, a patient can have re-

duced or altered responses, which can increase medical costs. The potential for pharmacokinetic interactions can also increase costs of medical care by requiring more frequent monitoring (including therapeutic drug monitoring) and assessment for dosage titration, side effect detection, and management of adverse effects. Finally, in the extreme case, increased costs can come from toxicity and the possible resultant hospitalization and destabilization of the medical problem.

Dose Dependency of Effects

It is important to understand that these effects, whether they are pharmacodynamic or pharmacokinetic, are dose related. Thus, it should be obvious that a low-potency drug can achieve the same effect as a high-potency drug. However, for the low-potency drug, the effect occurs at a higher dosage than for the high-potency drug. Conversely, a high-potency drug achieves the effect at a lower dosage than does the low-potency drug.

Prediction of Interactions

Both pharmacodynamic and pharmacokinetic drug interactions can be predicted by test tube assays, that is, by in vitro experiments. Pharmacodynamic interactions can be predicted from studies with transporters and receptors of neurotransmitters.[4] For pharmacokinetic drug interactions, researchers have been using liver microsomal enzymes as well as molecularly cloned enzymes expressed in nonliver cells to do these studies. From the information gleaned from these latter kinds of experiments, one can predict the likelihood that certain drugs will cause a pharmacokinetic interaction in patients.

PRIMER ON CLINICAL PHARMACOLOGY

When a clinical pharmacologist talks about pharmacokinetics, several variables are at issue. These variables include absorption, distribution, metabolism, and excretion of the drug. Rarely do pharmacokinetic interactions involve absorption. However, there are now some interesting examples of such an interaction involving psychotropic drugs.

The antibiotic rifampin is able to induce the activity of certain drug-metabolizing enzymes that are present in the liver and in the gut. Alprazolam, for example, which is metabolized by an enzyme (CYP3A4) that is induced by rifampin, when given to a patient who is taking rifampin, does not get into the blood very well because it is metabolized very rapidly at the site of absorption in the gut.[5]

Pharmacokinetic drug interactions also rarely affect the distribution or excretion of drugs. Most interactions are at the level of metabolism, which, as I mentioned, can occur in the gut, but usually occur in the liver. Recently, some of the drug-metabolizing enzymes that are present in the liver have been discovered in the brain,[6] suggesting that local metabolism occurs in this organ as well.

PHASE I AND II METABOLIC REACTIONS

Clinical pharmacologists also talk about different phases of drug metabolism, that is, phase I and phase II. Phase I reactions involve the hydrolysis, oxidation, and reduction of drugs. These reactions generally, but not always, change the drug into a more reactive form.

As mentioned previously, codeine is not a very active drug at opioid receptors. However, after it undergoes a phase I reaction, it is converted into the more active drug morphine. The enzymes involved in the metabolism of these drugs by phase I reactions have been called mixed function oxidases. The majority of these oxidases are the cytochrome P450 enzymes. There is more about cytochrome P450 enzymes below.

The phase II reactions are conjugation or synthetic reactions in which a molecule such as sulfate, glycine, or glucuronic acid is added to the drug. As a result, the compound is usually inactivated and is more polar, making it more readily excreted by the kidneys.

Phase I oxidation reactions occur through a large group of heme-containing enzymes called cytochrome P450 enzymes. Historically, the name comes from early research on these enzymes when biochemists purified these enzymes from the liver and discovered that they contained heme. One of the tests for heme is to expose the enzyme to carbon monoxide and measure its absorption of light. After this test was done for these enzymes, researchers found that the ultraviolet absorption of the reduced enzyme was at a wavelength of 450 nm, hence the number in the name.

Cytochrome P450 Enzyme Classification and Nomenclature

There are 2 major classes of cytochrome P450 enzymes. The enzymes of the first class metabolize endogenous substances (e.g., steroids) and are present in mitochondria. The second class comprises those enzymes that primarily metabolize xenobiotics (e.g., drugs) and are found in cellular smooth endoplasmic reticulum—primarily in the liver—but also in the gastrointestinal tract and the brain.

Within the second class (enzymes that metabolize xenobiotics), researchers have identified more than 30 human cytochrome P450 enzymes by molecular cloning techniques. Because of this large number of enzymes, researchers have devised a systematic nomenclature based on the amino acid sequence of these enzymes.[7] When a protein has been molecularly cloned, the DNA sequence is known. From this sequence, researchers can deduce the amino acid sequence from the genetic code. Thus, it is a simple matter to lump these enzymes by the homology of their amino acid sequences.

Accordingly, if a group of enzymes has 40% or greater amino acid homology, these enzymes are placed into a unique family. This family is given an arabic number.

Next, those enzymes in a family having 55% or greater sequence homology are placed into a subfamily, which is denoted by a capital letter. Further, within a subfamily, one can have different enzymes from different genes, which have very high sequence homology. These different gene products are given an arabic number. For example, the most widely studied of the P450 enzymes is CYP2D6, which means cytochrome P450 enzyme in family 2, subfamily D, and gene product 6.

All our available information, which is changing almost daily, suggests that from the standpoint of drug interactions with antidepressants, there are only a few of these cytochrome P450 enzymes that we need to be concerned about. They are from 3 families: 1 (CYP1A2), 2 (CYP2C9, CYP2C19, and CYP2D6), and 3 (CYP3A4). The most complete data are available for the following enzymes: CYP1A2, CYP2D6, and CYP3A4.

Polymorphisms of the Cytochrome P450 Enzymes

At another level, different from the simple assignment of an enzyme to a family, subfamily, and gene product, and adding further to the complexity of this topic, is the existence of different forms of a particular gene product. If the enzyme exists in different forms at a high enough percentage in the population, usually about 2%, it is said to be polymorphic, which means having multiple forms.

So far, researchers have discovered polymorphisms for at least 3 different enzymes. The most widely studied has been CYP2D6,[8] which metabolizes many drugs, including codeine, dextromethorphan, and tricyclic antidepressants. For example, 3% to 10% of whites and a small percentage (0% to 2%) of blacks and Asians have forms of CYP2D6 that have very little or no activity.[8,9] People who have a low-activity form of the enzyme are called poor metabolizers of the drugs that are metabolized by that enzyme. At CYP2C19, 3% to 5% of whites and blacks and 18% to 23% of Asians are poor metabolizers of certain drugs.[10–12] At CYP1A2, 12% to 13% of whites, blacks, and Asians are poor metabolizers of drugs such as caffeine.[13] Therefore, the vast majority of people are considered extensive metabolizers of those drugs metabolized by these enzymes. On the basis of these numbers, one can estimate that about 1 in 2000 white individuals is a poor metabolizer of drugs metabolized by all 3 of these enzymes.

THE 3 IMPORTANT ENZYMES: CYP1A2, CYP2D6, AND CYP3A4

The 3 enzymes for which the data are most extensive include CYP1A2, CYP2D6, and CYP3A4. A discussion follows of the most potent substrates and inhibitors of these enzymes, based upon in vitro data as well as a review of in vivo data supporting the effects of the most potent inhibitors. It is important to note that a drug can be both a substrate and an inhibitor of an enzyme. For example, nef-

azodone not only is metabolized by CYP3A4, but also is an inhibitor of this enzyme. However, in vivo, it is also possible that a metabolite is an inhibitor of the enzyme.

At this time, the ideal clinical experiments have not been done and may never get done. These experiments would be conducted in the same clinical laboratory among control subjects and would test "head-to-head" all the new antidepressants against specific drugs known to be metabolized by specific cytochrome P450 enzymes. These experiments would provide direct comparisons of inhibitory potencies of antidepressants. In the absence of these clinical data, in vitro data can be a guide.[1]

CYP1A2

The CYP1A2 enzyme metabolizes tricyclic antidepressants, the neuroleptic clozapine, some cardiovascular drugs, and other drugs such as caffeine, theophylline, and phenacetin. From in vitro studies, fluvoxamine is clearly the most potent inhibitor of this enzyme.[14,15] Therefore, fluvoxamine is considered a high-risk drug at the CYP1A2 enzyme. This means that for patients taking fluvoxamine, there is a high likelihood that this drug will inhibit the metabolism of those drugs metabolized by CYP1A2.

Imipramine is an example of a drug metabolized by CYP1A2, which demethylates this tricyclic antidepressant. Fluvoxamine's potent inhibitory effect on the metabolism of imipramine by this enzyme was readily shown in a clinical study of a group of subjects given a single dose of imipramine alone or after prior treatment with fluvoxamine.[16] This inhibition was apparent from the marked increase in the maximum concentration of imipramine in the blood and the much slower disappearance from the blood of this tricyclic antidepressant in the subjects who received fluvoxamine before the imipramine. The practical consequence of this interaction is that patients taking the combination of fluvoxamine and imipramine require a lower dosage of the tricyclic antidepressant to maintain a blood level within the therapeutic range compared with those patients not taking this combination.

CYP2D6

Another enzyme for which extensive data have been compiled is CYP2D6, which metabolizes a multitude of drugs including tricyclic antidepressants, some neuroleptics (e.g., haloperidol and risperidone), some cardiovascular drugs (e.g., encainide and flecainide), the antitussive agent dextromethorphan, and codeine. Quinidine, which is also a substrate for this enzyme, is by far the most potent inhibitor in vitro of CYP2D6.[15,17–25] But not too far behind in potency is paroxetine, whose inhibitory effects on this enzyme have been demonstrated in clinical studies.

In a recently published study, paroxetine was clearly shown to inhibit the metabolism of the tricyclic antidepressant desipramine.[26] After 24 hours of paroxetine treatment, there was a modest increase in the maximum con-

centration and the total concentration of desipramine in the systemic circulation, measured as the area under the curve (AUC) of a graph plotting plasma concentration over time. However, after only 1 day of treatment with paroxetine, steady state is not reached. Based on its elimination half-life, it takes about 4 to 5 days to reach steady state for paroxetine. However, at 10 days, which is clearly at steady state, there is nearly a 4-fold increase in both the maximum concentration and the AUC after the same dose of desipramine. Again, the practical implication for these results is that if a tricyclic antidepressant were combined with paroxetine, the dosage of the tricyclic antidepressant should be much lower than it would be when used singly. In addition, blood levels of the tricyclic antidepressant should be determined so that the therapeutic and not the toxic range is reached.

CYP3A4

CYP3A4 is another of those enzymes for which we have a great deal of data on substrates and inhibitors and for which there are some potentially very serious interactions. Specifically, there has been concern in the medical literature and at the Food and Drug Administration (FDA) about combining the antihistaminic drugs terfenadine (which was recently removed from the market because of these concerns), astemizole, or cisapride with other drugs that inhibit this enzyme. The specific concern relates to the cardiotoxic potential of these drugs, which are metabolized into noncardiotoxic derivatives by CYP3A4. These drugs at high enough concentrations can cause torsades de pointes, a potentially fatal supraventricular tachycardia that can lead to sudden death, even in the healthiest of individuals.

Some substrates for CYP3A4 include the antidepressants nefazodone and sertraline; the antihistaminics mentioned above; the sedative-hypnotics of the benzodiazepine class (e.g., alprazolam, clonazepam, and triazolam); and cardiovascular drugs, such as diltiazem and nifedipine.

By far the most potent drugs at inhibiting this enzyme are the antifungal agents ketoconazole and itraconazole.[15,21,27–30] Erythromycin is also a potent inhibitor. Of all the antidepressants, nefazodone is the most potent at inhibiting this enzyme. For this reason, the FDA has required Bristol-Myers Squibb to indicate in the package insert that nefazodone is contraindicated with astemizole, terfenadine, or cisapride, each of which can cause cardiac arrhythmias at high concentrations, which can be reached when the metabolism of these drugs is inhibited.

Clinical research clearly shows that nefazodone can inhibit the metabolism of a drug metabolized by CYP3A4. An example is a study with the CYP3A4 substrate alprazolam.[31] This benzodiazepine has a relatively short elimination half-life of about 2 hours. However, in combination with nefazodone, peak blood levels were nearly doubled and the elimination half-life was severalfold longer, indi-

cating a marked slowing of the clearance of the benzodiazepine by the antidepressant drug. Thus, nefazodone has converted alprazolam from a short-acting to a long-acting drug. Again, the practical consequence of this interaction is that a patient should be taking a much lower dosage of alprazolam in combination with nefazodone compared with the dosage for a patient taking alprazolam alone.

INFREQUENCY OF DRUG INTERACTIONS

It is common for patients to be treated with multiple drugs. However, in our clinical practices it is not common for us to observe a clinically significant drug interaction. Why might this be? There are many possible explanations for the apparent infrequency of drug interactions. One explanation concerns the concept of therapeutic index, which relates the dose (blood level) of a drug required to produce a therapeutic effect to that which causes an adverse effect. Many drugs have a wide therapeutic index, which means that there is a broad range for therapeutic blood levels and that very high levels are required to cause toxic effects. The converse is the case for drugs with a narrow therapeutic index. So, inhibiting the metabolism of a drug with a wide therapeutic index may not raise blood levels into the range of toxicity. Many of the drugs that patients are taking have large therapeutic indices; thus, inhibition of the metabolism of these drugs might not cause an adverse event. On the other hand, inhibition of the metabolism of a drug with a narrow therapeutic index will rapidly cause the levels to reach the toxic range.

Finally, there is a very interesting study that was published recently in *The Journal of Clinical Psychiatry*.[32] The study involved therapy with the combination of fluvoxamine and clomipramine for 22 patients who had refractory illness (mainly depression or obsessive-compulsive disorder). Patients were carefully assessed on multiple occasions for up to 4 weeks while taking this combination. Evaluations included plasma levels of the combination of clomipramine and its major metabolite, desmethylclomipramine; electroencephalograms; electrocardiograms; determinations of subjective adverse effects; and clinical global index at study end.

On 34 occasions during the 4 weeks of the study, patients had combined plasma concentrations of the parent compound and metabolite above 450 ng/mL, a level at which serious side effects have been reported. However, only about one third of the time at these levels did subjects have side effects, none of which were deemed serious by the authors. Nevertheless, 4 patients had "slight-to-moderate changes of intracardiac conduction." Also, at some time during this 4-week period, there were 28 occasions when patients had levels below 450 ng/mL. In this range, those with side effects totaled about 20%, a figure not very different from those occasions when patients had plasma levels above this level.

The study with fluvoxamine and clomipramine shows that in combination therapy, in which 1 drug inhibits the metabolism of another, it is possible to have levels of drug in the range where toxicity can occur, but in the absence of any clinical signs of toxicity. Depending upon the drug, the consequences could be minor. However, in the case of tricyclic antidepressants, which have arrhythmogenic effects at high levels, the result could be very serious. In addition, this study clearly shows that fluvoxamine, which is classified as having a high likelihood of inhibiting the metabolism of other drugs, does indeed inhibit the metabolism of clomipramine in most cases.

CONCLUSIONS

In conclusion, pharmacokinetic drug interactions of antidepressants are a *potential* and not a *certain* problem. These interactions are more likely to occur with high-risk drugs such as nefazodone, at CYP3A4; fluoxetine and paroxetine, at CYP2D6; and fluvoxamine, at CYP1A2. They are less likely to occur with low-risk drugs such as venlafaxine, sertraline, and probably bupropion and mirtazapine. However, drug interactions may occur even with low-risk drugs, and we therefore need to be vigilant in our awareness of the possibility that these interactions may occur.

Drug names: alprazolam (Xanax), astemizole (Hismanal), bupropion (Wellbutrin), cisapride (Propulsid), clomipramine (Anafranil), clonazepam (Klonopin), clozapine (Clozaril), desipramine (Norpramin and others), diltiazem (Cardizem), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), imipramine (Tofranil and others), itraconazole (Sporanox), ketoconazole (Nizoral), nefazodone (Serzone), nifedipine (Adalat, Procardia), paroxetine (Paxil), rifampin (Rifadin, Rimactane), risperidone (Risperdal), sertraline (Zoloft), terfenadine (Seldane), triazolam (Halcion), venlafaxine (Effexor).

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