Drug Interactions With Newer Antidepressants: Role of Human Cytochromes P450

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Selective serotonin reuptake inhibitors and related antidepressant compounds have the secondary pharmacologic property of inhibiting the activity of human cytochrome P450 enzymes responsible for the oxidative metabolism of many drugs. A number of clinically important pharmacokinetic drug interactions are a consequence of these cytochrome inhibiting effects. This review evaluates the clinical implications of the metabolic profiles of the newer antidepressants, the relative activities of various new antidepressants as inhibitors of human cytochrome P450, and the various in vivo and in vitro methodologies that can be used for identification and quantification of drug interactions.

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The selective serotonin reuptake inhibitor (SSRI) and related "mixed mechanism" antidepressants are not clearly superior to traditional antidepressants in terms of therapeutic efficacy,[1–3] but the profile of clinical pharmacologic properties and side effects of these newer compounds clearly differs from that of the older antidepressants.[4–16] Of particular importance is the capacity of SSRIs and related antidepressants to inhibit the activity of human cytochrome P450 enzymes responsible for the oxidative biotransformation of many drugs used in clinical practice.[17–24] The possibility of pharmacokinetic drug interactions must be carefully considered during clinical use of the current generation of antidepressants. This is a complex problem, since each new antidepressant and/or its pertinent in vivo metabolites can be anticipated to have a different activity or potency as an inhibitor of each specific human cytochrome. Understanding of the clinical issues has been helped by advances in the discipline of cytochrome chemistry, including the biochemistry, molecular genetics, and clinical functions of the human cytochromes P450.[25–31] Most clinical observations and studies of drug interactions with new antidepressants are in fact largely consistent with models based on molecular and in vitro data.[32–36] This field is advancing so rapidly that secondary sources as well as approved labeling language may be out of date or not in context. Review articles, product labeling information, and promotional material therefore should be evaluated critically, and recent primary sources consulted whenever possible.

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METABOLISM OF ANTIDEPRESSANTS IN HUMANS

Clinically important metabolic products of some newer antidepressants are listed in Table 1. Among the SSRIs, fluoxetine, sertraline, and citalopram all undergo *N*-demethylation in humans; the respective metabolites are norfluoxetine, desmethylsertraline, and monodesmethylcitalopram.[19–24,37,38] Some of these metabolites appear in plasma at levels similar to or higher than those of the parent drug, and the metabolites have values of elimination half-life longer than those of the respective parent compounds. Fluoxetine and norfluoxetine are similar to each other in SSRI activity,[38] as are citalopram and monodesmethylcitalopram.[39,40] Therefore parent drug and principal metabolite both contribute to clinical efficacy and

side effects during clinical treatment with fluoxetine or citalopram. In addition, fluoxetine and norfluoxetine both have cytochrome-inhibiting activity, and both will contribute to pharmacokinetic drug interactions. However, citalopram and monodesmethylcitalopram have weak or negligible cytochrome inhibiting activity. Desmethylsertraline, the principal metabolite of sertraline, has only weak SSRI activity compared to its parent compound[41]; both have equivalent, although generally weak, cytochrome inhibiting activity. In the case of paroxetine and fluvoxamine, clinically important metabolites in human plasma have not been identified.[42,43]

Nefazodone has the most complex metabolic profile among the "mixed-mechanism" antidepressants.[44] Nefazodone undergoes parallel biotransformations, yielding: (1) hydroxy products formed by hydroxylation at 2 sites on the molecule; (2) a triazoledione derivative; and (3) metachlorophenylpiperazine (*m*CPP) following cleavage of the molecule.[45,46] The triazoledione and the aliphatic hydroxy metabolite are present in human plasma in significant concentrations during chronic treatment with nefazodone, whereas *m*CPP levels are relatively low.[46] The antidepressant activity of the metabolites of nefazodone is not established. Venlafaxine is biotransformed by parallel demethylation reactions at 2 sites on the molecule.[47] The *O*-desmethyl derivative appears in plasma in levels exceeding those of the parent drug,[48,49] and both compounds have antidepressant activity. *N*-desmethylvenlafaxine is a relatively minor metabolite. Mirtazapine is biotransformed to *N*-desmethylmirtazapine as the principal metabolite.[50]

Table 1. Newer Antidepressants, Their Principal Metabolic Products, and Cytochromes Responsible for Biotransformation*

Parent Compound	Important Metabolite(s)	Responsible Cytochrome(s)
Predominant SSRI Mechanism		
Fluoxetine	Norfluoxetine	2C9 (3A, 2D6)
Sertraline	Desmethylsertraline	2C9, 3A (others not established)
Citalopram	Monodesmethylcitalopram (Didesmethylcitalopram)	2C19, 3A (2D6)
Paroxetine	None described to date	2D6
Fluvoxamine	None described to date	1A2, 2D6
"Mixed" Mechanism		
Nefazodone	Triazoledione	3A
	Hydroxynefazodone	3A
	(*m*CPP)	3A
Venlafaxine	*O*-Desmethylvenlafaxine	2D6
	(*N*-Desmethylvenlafaxine)	3A, 2C19
Mirtazapine	Desmethylmirtazapine	3A (1A2, 2D6)
	(8-Hydroxymirtazapine)	2D6 (1A2)
	(Mirtazapine *N*-oxide)	3A (1A2)

*Parentheses indicate metabolic products of relatively small quantitative importance.

Table 2. Representative Index Reactions and Specific Chemical Inhibitors for Studies of Human Cytochromes P450

Cytochrome P450	Index Substrates	Specific Inhibitor
1A2	Phenacetin	α-Naphthoflavone; furafylline[a]
	Caffeine	
2C9	Phenytoin	Sulfaphenazole
	Tolbutamide	
2C19	*S*-Mephenytoin	Omeprazole[b]
2D6	Dextromethorphan	Quinidine[c]
	Desipramine	
	Bufuralol	
	Sparteine	
	Debrisoquin	
2E1	Chlorzoxazone	Diethyldithiocarbamate[a,c]
3A	Midazolam	Ketoconazole[c]; troleandomycin (TAO)[a]; gestodene[a]
	Triazolam	
	Alprazolam	
	Testosterone	
	Nifedipine	

[a]Mechanism-based inhibitor.
[b]Suitable as specific inhibitor in vitro (up to 10 μM); less suitable in vivo due to metabolite, omeprazole sulfone.
[c]Suitable for human in vivo studies.

IDENTIFICATION OF RESPONSIBLE CYTOCHROMES

Knowledge of the specific human cytochromes mediating biotransformation of antidepressants allows health care professionals to anticipate a number of clinically important factors contributing to regulation of metabolism of the antidepressants. Examples of such factors include the possibility of genetic polymorphism, as occurs with drugs metabolized by P450 2D6 or 2C19[51–59]; the possibility of extrahepatic contributions to metabolism as occurs with substrates of P450 3A that may be biotransformed in part in the gastrointestinal tract mucosa; and the profile of other compounds that may induce or inhibit metabolism (Table 2).

Research Methods

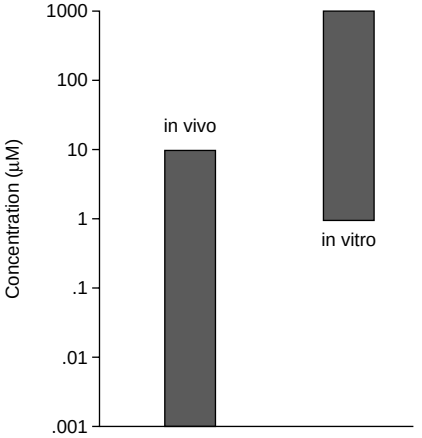
Cytochrome identification may be accomplished through a combination of clinical pharmacologic approaches as well as in vitro models. For specific cytochromes (P450 2C19 or 2D6) whose activities are regulated by a genetic polymorphism, that cytochrome may be inferred to participate in clearance of the drug under study, if that drug's clearance cosegregates with the clearance or metabolic ratio of a test substrate for the corresponding cytochrome, such as dextromethorphan for 2D6 or *S*-mephenytoin for 2C19. This population cosegregation approach has provided important data, but also has limitations and drawbacks. It is useful only when metabolism is mediated by polymorphically regulated cytochromes and qualitative (but not quantitative) contributions of a specific cytochrome can be identified. Furthermore, the method is indirect, and assumes that subject groups divided as "normal" and "slow" metabolizers are otherwise comparable with respect to activity of all other cytochromes. Confounded associations cannot be excluded and may lead to misidentification of responsible cyto-

chromes. Conclusions based on plasma concentrations of metabolites as opposed to parent drug may also be confounded, since the area under the plasma concentration curve for a metabolite depends on both its rate of formation from the parent compound as well as its own clearance, which may be mediated by a different cytochrome. A controlled crossover study of clearance of the drug in question, with and without coadministration of specific chemical inhibitor (Table 2), may presumptively identify the corresponding cytochrome if clearance is substantially reduced by the specific inhibitor. However such inhibitors must be safe and appropriate for clinical use, as well as have reasonable inhibitory specificity for the cytochrome in question.

In vitro models are being increasingly applied to identification of cytochromes mediating specific metabolic biotransformations.[25–36] Microsomal preparations of human liver in vitro contain the various human cytochromes in proportion to their quantitative representation in human liver in vivo. The capacity of a relatively specific chemical inhibitor (Table 2) to inhibit biotransformation of a specific substrate to its initial metabolite constitutes evidence supporting the participation of the corresponding cytochrome. The in vitro approach using chemical inhibitors has the obvious advantages over clinical studies of being less costly, more rapid in implementation, free of risk of human drug exposure, as well as offering a larger number of potential chemical inhibitors for this purpose and the possibility of assigning both quantitative and qualitative contributions of specific cytochromes. Antibodies with relatively specific inhibitory activity against the various human cytochromes can also be used to support or confirm data from in vitro chemical inhibition studies.[60] In recent years, the versatility of in vitro models has been increased by the availability of microsomes containing pure human cytochromes as expressed by cDNA-transfected human lymphoblastoid cells,[61] or other expression systems.[62]

Among the limitations of in vitro approaches is the need to utilize substrate concentrations that are one or more orders of magnitude higher than those encountered clinically, even accounting for the extensive uptake of some lipophilic drugs into liver that produces intrahepatic concentrations higher than those in plasma (Figure 1). In vitro studies of high substrate concentrations can be extrapolated down to a clinically relevant concentration range as long as mathematical models remain valid over the entire range.[63] However, a "high-affinity" metabolic reaction (i.e., one with a low K_m) that contributes importantly to a drug's biotransformation at clinically relevant concentrations could be overlooked or underestimated in vitro if assay sensitivity limits impede study of substrate concentrations in that low range. The specificity of chemical inhibitor probes is of concern for in vitro as well as in vivo models. No inhibitory probe is completely specific for its corresponding cytochrome—all ultimately become

Figure 1. Schematic Representation Showing a Typical Range of Antidepressant (and Metabolite) Concentrations Encountered in Human Plasma and Liver In Vivo, Compared With the Range Typically Studied Using In Vitro Models

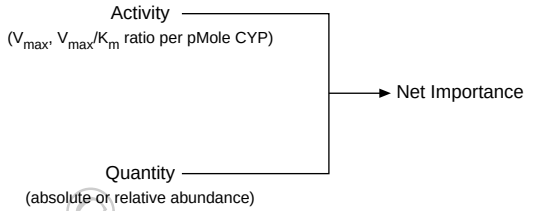


nonspecific at higher concentrations.[64] Ketoconazole, for example, has a relatively high specificity as an index inhibitor for P450 3A, as long as concentrations are below 1.0 µM; at higher concentrations specificity diminishes.[64–66] Omeprazole appears to have acceptable specificity as a P450 2C19 inhibitor at concentrations up to 10 µM. Above this range, specificity diminishes.[67] In vivo, omeprazole is biotransformed to a sulfone metabolite that has P450 3A inhibiting capacity. The SSRI fluvoxamine is not specific enough to serve as an index inhibitor, since it has moderate to strong inhibitory activity against P450 1A2, 2C19, 2C9, and 3A. Finally, the inferential strength of data from cDNA-expressed human cytochromes must be weighed against the intrinsic (and deliberate) limitations imparted by study of a single cytochrome removed from its usual cytochrome "mix." Studies of individual cytochromes can yield specific quantitative data on their activity as mediators of a specific reaction. However, an inference about the relative activity of different cytochromes either in vivo, or in liver microsomes in vitro, requires an independent estimate of the relative quantitative abundance of the cytochromes in question (Figure 2).[61]

Cytochromes Mediating Biotransformation of Antidepressants

In vivo and in vitro studies have collectively provided estimated contributions of specific cytochromes to the metabolism of the newer antidepressants (Table 1). Clearance of fluoxetine in human subjects cosegregates with the P450 2D6 metabolic polymorphism, suggesting the conclusion that fluoxetine clearance is mediated by that cytochrome.[68] In vitro, however, 2D6 appears to be relatively unimportant, whereas 2C9 is the principal cytochrome, with a possible further contribution of 3A.[69,70] The discrepancy between in vivo and in vitro results could be ex-

Figure 2. The Net Importance of a Specific Cytochrome as a Contributor to a Metabolic Biotransformation In Vivo, or in Liver Microsomal Preparations In Vitro, Depends on Two Factors*



*The two factors are the activity of that cytochrome as a mediator of the reaction, related to the V_{max} and to the V_{max}/K_m ratio (intrinsic clearance), and the quantitative abundance of that cytochrome.

plained by a confounded association of 2D6 phenotype in vivo with extremes in 2C9 activity. The in vitro methods may also have overlooked the participation of a low K_m (high-affinity) reaction mediated by P450 2D6 at low substrate concentrations that cannot be reliably studied. Sertraline clearance in vivo did not cosegregate with 2D6 metabolizer phenotype,[68] but the cytochromes contributing to its metabolism are not clearly established. P450 2C9 and 3A are likely to be involved to some degree, but the other contributing cytochromes are not known. Data on paroxetine and fluvoxamine are mostly indirect. Clearance of paroxetine cosegregates with 2D6 phenotype in vivo[71,72]; involvement of 2D6 is also supported by in vitro data.[73] Fluvoxamine clearance is associated with 1A2 and 2C9 activity in vivo, based on population cosegregation data,[74,75] as well as the observation of induced fluvoxamine clearance in cigarette smokers.[76] Biotransformation of citalopram to monodesmethylcitalopram depends on both 3A and 2C19 in vitro, with a possible small contribution of 2D6[77,78]; citalopram clearance in vivo cosegregates with 2C19 phenotype.[38] Nefazodone clearance is essentially completely dependent on P450 3A, based on in vitro data.[79] Formation of the principal metabolite of venlafaxine (*O*-desmethylvenlafaxine) is dependent mainly on 2D6; production of *N*-desmethylvenlafaxine, the minor metabolite, depends on a combination of 3A and 2C19.[80,81] Formation of the principal demethylated product of mirtazapine is mediated mainly by 3A, with additional contributions of 1A2 and 2D6.[50]

INHIBITION OF HUMAN CYTOCHROME ACTIVITY BY ANTIDEPRESSANTS

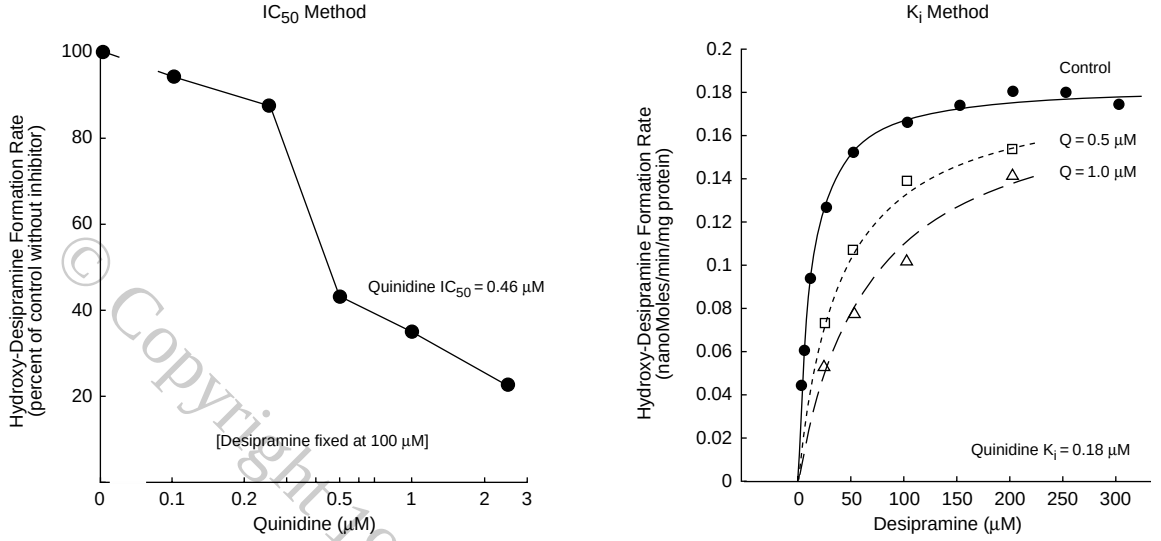
Research Methods

In vivo and in vitro approaches similar to those used for cytochrome identification are applicable to evaluation of antidepressants and their metabolites as potential inhibitors of specific human cytochromes. A controlled clinical pharmacokinetic study design, in which clearance of an index substrate (Table 2) is determined with and without coadministration of the antidepressant in question, directly addresses the question in the human context. However, such studies have drawbacks, since they are costly, time-consuming, and involve finite (although small) risks of human drug exposure. Furthermore when the antidepressant being studied undergoes in vivo biotransformation itself,[82] any metabolic inhibition that is observed could be due to parent drug, metabolites, or both. There is no direct method to resolve the relative contributions of multiple potential inhibitors that are present simultaneously, nor of estimating the quantitative inhibitory potency of any one inhibitor.

Using in vitro models of human liver microsomes, a series of drugs and/or their metabolites can be screened relatively quickly at low cost, and with no human drug exposure, to determine quantitative inhibiting potency against specific index reactions presumed to reflect the activity of specific cytochromes with relatively high specificity (Table 2).[32,36,83] One approach uses a fixed concentration of the index substrate coincubated with variable concentrations of the inhibitor. The relation of decrement in metabolite formation rate versus inhibitor concentration yields an estimate of a 50% inhibitory concentration (IC_{50}) (Figure 3). Values of IC_{50} are suitable for comparing the relative potency of a series of inhibitors, and are independent of the specific biochemical mechanism of inhibition. On the other hand, IC_{50} values depend on substrate concentration when inhibition is competitive, and cannot be directly applied to in vitro-in vivo scaling models, except when inhibition is established as having a noncompetitive mechanism.

A second approach utilizes the inhibition constant (K_i), which reflects inhibitory potency in reciprocal fashion. Determination of K_i involves more work, time, and expense, since it requires study of multiple substrate concentrations and multiple inhibitor concentrations (Figure 3). K_i is model-dependent, since it depends upon the specific mechanism of inhibition,[84] which may not be established. Once determined, K_i is independent of substrate concentration and can be used under some defined conditions for quantitative in vitro-in vivo scaling of drug interactions.[32–36] Although K_i is less than or equal to IC_{50} as a general rule, K_i will be equal to IC_{50} if inhibition is noncompetitive, or if inhibition is competitive and the substrate concentration is far below the reaction K_m. K_i and IC_{50} both provide similar estimates of relative inhibitory potency for a series of inhibitors of a specific reaction, but the absolute values of K_i and IC_{50} do not cross different substrates for the same cytochrome. As an example, the inhibitory K_i values for SSRIs versus sparteine oxidation[85] do not equal the corresponding K_i values versus desipramine hydroxylation,[65,86] although the 2 metabolic reactions are mediated mainly by 2D6. However the relative inhibitory potency should be maintained across substrates for the same cytochrome.

Figure 3. Comparison of Two In Vitro Methods for Determining the Inhibitory Potency of Quinidine Versus Desipramine Hydroxylation, a Reaction Mediated Mainly by Cytochrome P450 2D6*



*Studies were performed using microsomal preparations from human liver.
Left: A fixed concentration of desipramine (100 µM), considerably higher than the K_m value of 10.2 µM, was incubated with varying concentrations of quinidine. Reaction velocities were expressed as a percentage of the control value without inhibitor. Nonlinear regression was used to determine the quinidine IC_{50} value of 0.46 µM.
Right: Varying concentrations of desipramine were incubated with liver microsomes in the control conditions (without inhibitor), and with coaddition of two concentrations of quinidine. Control data were analyzed by nonlinear regression to determine the reaction V_{max} and K_m. Data with coaddition of quinidine were analyzed under the assumption of Michaelis-Menten kinetics with competitive inhibition. Note that the K_i value for quinidine is smaller than the IC_{50} value.

Table 3. Inhibition of Human Cytochromes P450 by Newer Antidepressants*

	Cytochrome P450					
Antidepressant	1A2	2C9	2C19	2D6	2E1	3A
Fluoxetine	+	++	+ to ++	+++	—	+
Norfluoxetine	+	++	+ to ++	+++	—	++
Sertraline	+	+	+ to ++	+	—	+
Desmethylsertraline	+	+	+ to ++	+	—	+
Paroxetine	+	+	+	+++	—	+
Fluvoxamine	+++	++	+++	+	—	++
Citalopram	+	0	0	0	0	0
Desmethylcitalopram	0	0	0	+	0	0
Nefazodone	0	0	0	0	—	+++
Triazoledione	0	0	0	0	—	+
Hydroxynefazodone	0	0	0	0	—	+++
Venlafaxine	0	0	0	0	—	0
O-Desmethylvenlafaxine	0	0	0	0	—	0
Mirtazapine	0	—	—	+	—	0

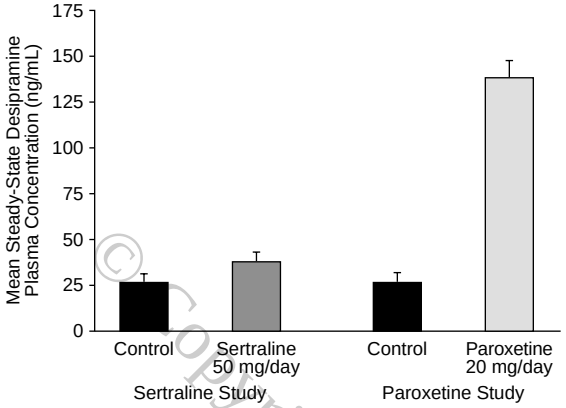
*0 = minimal or zero inhibition; + = mild inhibition; ++ = moderate inhibition; +++ = strong inhibition. Dash (—) indicates no data available.

Review of the Data Base (Table 3)

All sources consistently identify fluvoxamine as a highly potent inhibitor of P450 1A2,[66,87,88] causing large reductions in clearance of 1A2 substrates such as caffeine, clozapine, tacrine, and chloroguanide.[89–93] Although no systematic study has been published, a significant interaction of fluvoxamine with theophylline should be anticipated. Some of the other antidepressants show a weak to moderate capacity to inhibit 1A2 in vitro,[66] but significant interactions in vivo are not clearly documented. Fluvoxamine also is the most potent of the newer antidepressants as an in vitro inhibitor of P450 2C9.[94] Labeling information describes a highly significant interaction of fluvoxamine with warfarin in a controlled pharmacokinetic study, but no published data are available. Fluoxetine (in particular the *S*-enantiomer) also is a significant 2C9 inhibitor in vitro,[94] and a number of case reports describe interactions with phenytoin in vivo.[95] Sertraline and desmethylsertraline are weak 2C9 inhibitors in vitro,[94] and sertraline did not interact with tolbutamide or phenytoin in vivo.[96,97] Nefazodone also produced no interaction with phenytoin in a clinical study.[98] Fluvoxamine is a highly potent inhibitor of 2C19, and significant interactions with 2C19 substrates should be anticipated in vivo.[93,99,100] Some of the other antidepressants demonstrate some degree of 2C19 inhibition in vitro, but the clinical significance of this is not established.

Inhibition of P450 2D6 activity by newer antidepressants is a topic receiving considerable attention in pharmaceutical promotional materials, which not uncommonly encourage the implication that inhibition of 2D6 by SSRIs is not clinically important, or that differences among SSRIs are unclear or indistinct. Particular studies or results may be cited out of their proper context to support this view. However, the scientific data on antidepressants and P450 2D6 are unequivocal, with close agreement of in vitro and in vivo results.[32,65,86] Fluoxetine, norfluoxetine,

Figure 4. Mean ± SE Steady-State Plasma Desipramine Concentrations in Studies of Human Volunteer Subjects*



*Adapted in part from reference 104. One group of volunteers received desipramine 50 mg daily in the control condition and with coadministration of sertraline 50 mg daily. A second group of volunteers received the same dose of desipramine in the control condition, and with coadministration of paroxetine 20 mg daily. Sertraline causes a small and statistically significant increase in plasma desipramine levels, whereas paroxetine causes a very large increase. The differential inhibition of desipramine clearance by sertraline and paroxetine in vivo is entirely consistent with changes anticipated based on in vitro studies.

and paroxetine are highly potent inhibitors of P450 2D6.[65,86,101,102] Usual therapeutic doses of fluoxetine or paroxetine, producing a usual range of steady-state plasma concentrations, typically impair clearance of 2D6 substrates such as desipramine by 70% or more, with steady-state plasma desipramine concentrations increasing 4-fold or more (Figure 4).[102–108] Interactions of this magnitude obviously are of clinical importance.[102] In contrast, sertraline, desmethylsertraline, and fluvoxamine have nearly an order of magnitude lower potency as 2D6 inhibitors than do fluoxetine, norfluoxetine, and paroxetine.[65,86] Coadministration of sertraline with desipramine will increase steady-state desipramine concentrations by 20% to 50%, depending on the daily dose and plasma concentration of sertraline (and desmethylsertraline) (Figure 4).[103,104,108] Citalopram, nefazodone, venlafaxine, and mirtazapine are at most weak 2D6 inhibitors.[50,80,89,101,109,110] It should be emphasized that inhibition of 2D6 activity will be evident only in subjects of the genetically "normal" metabolizer phenotype. Genetically "poor" metabolizers lack functional enzyme and already have low clearance of 2D6 substrates regardless of inhibitor coadministration.[105,111]

Biotransformation of drugs by cytochrome P450 3A is strongly inhibited by nefazodone both in vitro[79,112] and in vivo.[113,114] In clinical studies, nefazodone produces large decrements in clearance of 3A substrates such as alprazolam and triazolam.[113,114] Inhibition is attributable to nefazodone itself and to the hydroxylated metabolite, but not to the triazoledione metabolite or to *m*CPP.[79] Among the other antidepressants, fluoxetine itself is a weak 3A inhibitor, but *N*-demethylation of this compound to form norfluoxetine results in moderate 3A inhibiting potency. This is a consistent finding across many in vitro studies (see review in reference 23). In clinical studies, coadministration of fluoxetine with substrates biotransformed partly or entirely by P450 3A isoforms (such as diazepam, alprazolam, carbamazepine, and amitriptyline) causes impaired clearance and elevated plasma concentration of these substrates (reviewed in reference 23). Some publications encourage the incorrect conclusion that fluoxetine and norfluoxetine are unlikely to be clinically important 3A inhibitors.[115,116] In any case it is clear that inhibition of 3A activity in vivo by fluoxetine, when it occurs, is attributable mainly to norfluoxetine,[23] which reaches significant plasma concentrations when fluoxetine treatment proceeds for a period of time.[19,20] A reported noninteraction of fluoxetine and terfenadine, for example, is attributable to the relatively low plasma norfluoxetine concentrations in the study participants,[116] inasmuch as norfluoxetine clearly inhibits terfenadine metabolism in vitro.[117] When fluoxetine treatment is discontinued, 3A inhibition may persist for some time thereafter due to slow elimination of norfluoxetine.[118] Understanding of 3A inhibition by fluoxetine is nonetheless incomplete, since fluoxetine did not importantly inhibit triazolam clearance[119] despite adequate plasma norfluoxetine levels and clear evidence of inhibition in vitro.[112] Sertraline, desmethylsertraline, and paroxetine are weak 3A inhibitors in vitro.[86] Sertraline produces small or undetectable clinical interactions with 3A substrates such as diazepam,[120] alprazolam (S. H. Preskorn, M.D., et al., unpublished data), and carbamazepine[121]; paroxetine produced no interaction with terfenadine. Fluvoxamine is a moderate 3A inhibitor in vitro[86] and in vivo.[122,123] Citalopram (L. L. von Moltke et al., unpublished data), venlafaxine,[109,124] and mirtazapine[50] are weak or negligible 3A inhibitors.

Citalopram and monodesmethylcitalopram are negligible inhibitors of P450 2E1 (L. L. von Moltke et al., unpublished data). The activity of other antidepressants as inhibitors of P450 2E1 has not been determined.

COMMENT

The new generation of antidepressant agents made available over the last decade has broadened the therapeutic options for depressive illness, but also poses new complexities in terms of differences among drugs in metabolic disposition as well as the propensity to produce drug interactions. Treatment of depression in the current era requires application of therapeutic skills together with principles of clinical pharmacology. The use of multiple medications by depressed patients may contribute to increasing the probability of drug toxicity due to drug interactions. Clinicians can utilize in vitro and in vivo data to make a more informed choice among the newer antidepressants and anticipate and avoid possible drug interactions.[83,102,125]

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlorzoxazone (Paraflex), citalopram (Celexa), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), ketoconazole (Nizoral), midazolam (Versed), nefazodone (Serzone), nifedipine (Adalat, Procardia), omeprazole (Prilosec), paroxetine (Paxil), phenytoin (Dilantin and others), sertraline (Zoloft), terfenadine (Seldane), tolbutamide (Orinase), triazolam (Halcion), venlafaxine (Effexor).

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