Clinical Pharmacokinetics of Fluvoxamine: Applications to Dosage Regimen Design

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Background: The disposition characteristics and pharmacokinetic parameters of drugs provide fundamental data for designing safe and effective dosage regimens. A drug's volume of distribution, clearance, and the derived parameter, half-life, are particularly important, as they determine the degree of fluctuation between a maximum and minimum plasma concentration during a dosage interval, the magnitude of the steady-state concentration, and the time to reach a steady-state plasma concentration upon chronic dosing. Potential drug-drug interactions can be predicted with knowledge of affinities for various cytochrome P450 (CYP) isozymes. ***Method:*** The literature was searched for information related to the pharmacokinetic properties of fluvoxamine and reports of its involvement in drug interactions. ***Results:*** The primary pharmacokinetic variables for fluvoxamine have been estimated in single and multiple dose studies in animals, healthy volunteers, and patients. Fluvoxamine is well absorbed after oral administration, widely distributed in the body, and eliminated with a mean half-life of 15 hours and a range from 9 hours to 28 hours. Its disposition is altered in hepatic, but not renal, disease. Data from elderly subjects reflect a modest need for dosage adjustment in this population. Fluvoxamine produces no active metabolites. The specific cytochrome isozymes involved in the hepatic elimination of the drug are undefined. Data from studies relating the plasma concentration of fluvoxamine to its clinical effects do not support routine plasma concentration monitoring in depression or anxiety disorders. Fluvoxamine has prominent affinity for the CYP1A2 isozyme, lesser affinity for the CYP3A4 and CYP2C isozymes, and minimal affinity for CYP2D6. This profile suggests the need for careful dosage adjustment when used together with some drugs that have a narrow therapeutic range in order to minimize inhibiting their metabolism. ***Conclusion:*** Overall, the pharmacokinetic profile of fluvoxamine is adequately defined to provide guidelines for developing safe and effective dosage regimens for most types of patients.

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The serotonin selective reuptake inhibitors (SSRIs) have many similarities in their preclinical pharmacology and in their spectrum of therapeutically useful effects despite a large diversity in their chemical structures. Fluvoxamine is the SSRI that has been available longer for clinical use than the other compounds in its class, having been introduced in Great Britain in 1983. Its pharmacokinetic properties have been summarized in several reviews.[1–4] Fluvoxamine exhibits meaningful differences compared with other SSRIs in the pharmacologic activity of its metabolites, its degree of binding to plasma proteins, its stereochemistry, and its affinity for various cytochrome P450 (CYP) enzymes. These characteristics have significance for guiding the clinical use of fluvoxamine.

Certain pharmacokinetic information is essential before a new drug is marketed in order to properly construct a dosage regimen that will result in sufficient drug exposure to the individual to produce therapeutic effects without overexposure that might cause adverse events. This information is summarized in Table 1. It is also desirable to have some knowledge of the disposition of a drug in special circumstances to guide dosage regimen design in the elderly, adolescents, or lactating women. These populations do not typically receive a new drug in premarketing trials (Phases I, II, III) but are likely to be exposed in Phase IV of drug development once prescribing of the drug is widespread. Rarely is the requisite information available at the time of marketing to guide clinical use in all circumstances. Useful pharmacokinetic data usually continue to become available throughout the effective lifetime of a drug. This review will update the clinical pharmacokinetic properties of fluvoxamine. Additional comments are made to place the role of pharmacokinetic investigations into a clinical perspective.

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Table 1. Pharmacokinetic Parameters Used to Define a Drug

Animal and Human Pharmacokinetic Parameters	Disease States and Other Conditions Affecting Disposition
Absorption	Hepatic function
Absolute bioavailability	Renal function
Time of peak plasma concentration	Smoking
Maximum plasma concentration	Age (young and old)
Distribution	Gender
Volume of distribution	Pregnancy
Plasma protein binding	Placental transfer
Blood and tissue to plasma concentration ratio	Lactation
Metabolism	Effective concentrations in patients
Metabolite identification and activity	Toxic concentrations
Enzymes mediating biotransformation	Concomitant drug therapy
Affinity for specific isozymes	
Elimination	
Renal excretion	
Clearance	
Half-life	

Table 2. Summary of Pharmacokinetic Parameters of Fluvoxamine*

Bioavailability:		
C_{max}:[a]	Mean: 17 ng/mL	Range: 8 to 28 ng/mL
T_{max}:	Mean: 5 hours	Range: 2 to 8 hours
Percent absorbed:	Assumed to be completely absorbed orally but bioavailability reduced to 53% due to first-pass metabolism in the liver	
Half-life:	Mean: 15 hours	Range: 9 to 28 hours
Clearance:	Mean: 80 L/hr	Range: 33 to 220 L/hr
Volume of distribution:	Mean: 5 L/kg	
Plasma protein binding:	Mean: 77%	
Active metabolites:	None	
Stereoisomerism:	None	
Changes in hepatic impairment:	Minimal	
Changes in renal impairment:	Minimal	
Breast milk secretion:	Minimal excretion	
Average steady-state concentration:[b]	20–500 ng/mL	
Therapeutic plasma concentration:	Not established; no demonstrated value in plasma concentration monitoring	

*Data based on references 3 and 5–7.
[a]50-mg dose.
[b]Expected range for most patients receiving effective doses from 200–300 mg/d.

PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters of a new drug are usually estimated first in animals, followed by Phase I studies in humans. This phase of drug development usually includes single dose administration to establish tolerance and safety and gain essential pharmacokinetic information to guide dosage regimen design during subsequent multiple dose studies. The fundamental pharmacokinetic properties of fluvoxamine are summarized in Table 2. These values are taken from studies reported in normal healthy volunteers and patients with hepatic cirrhosis.[3,5,8–10]

Absorption

Fluvoxamine is well absorbed after oral administration. In ascending oral doses between 25 and 100 mg of fluvoxamine administered in a solution, the time maximum concentration occurred was between 2 and 8 hours with a mean of around 5 hours.[5] These data suggest that absorption occurred relatively slowly, but a proportional increase in plasma concentration occurred with dose suggesting that the size of the dose had no effect on the amount of drug absorbed. This test of linearity is important in predicting that the total milligram daily drug dose will result in a similar systemic exposure of the drug regardless of the number or size of individual doses administered over the period of a day. For example, there should be no change in the total absorption of fluvoxamine whether given in a regimen of 100 mg once daily or 50 mg twice daily. However, information provided by the manufacturer of fluvoxamine showed that the drug exhibited nonlinear pharmacokinetics over a dose range of 100, 200, and 300 mg/day with the higher doses producing disproportionately higher concentrations than predicted from the lower dose.[9]

Absolute bioavailability, i.e., 100% systemic absorption, can only be confirmed by finding that the area under the plasma concentration versus time curve (AUC) after an oral dose is equivalent to the AUC obtained after an intravenous dose when clearance remains constant. This type of study has not been performed with fluvoxamine. Nevertheless, conclusions about oral absorption can be made from a study of radioactivity in the urine after administering a C^{14} radiolabeled dose orally.[8,11] Only drug molecules that are absorbed through the gastrointestinal tract can appear in the urine. Any unabsorbed radioactive drug would be excreted in the feces. Therefore, the amount of radioactivity recovered in the urine as a proportion of the administered dose can serve as an estimate of bioavailability. However, this estimate does not exclude drug from being metabolized on its first pass through the liver to metabolites that retain measurable radioactivity. Data from this type of study found that an average of 94% of fluvoxamine-related products was recovered in the urine.[11] Thus, fluvoxamine may be nearly completely absorbed after oral administration, but the absolute bioavailability, i.e., the amount reaching the systemic circulation in an intact form, is approximately 53%.[11] Fortunately, the coadministration of food, a potential source of variability in the absorption of drugs, did not interfere with the absorption of fluvoxamine.[6]

Distribution

The distribution characteristics of drugs in development should be assessed in order to determine if the drug reaches the target organ or tissue and to learn whether any specific organs accumulate drug excessively that might suggest an unusual potential for toxicity. An example of

this latter phenomenon occurs with the antimalarial drug chloroquine. When used in high daily doses above 250 mg, irreversible retinopathy has occurred presumably because of deposition of the drug in melanin-rich ophthalmic tissue.[12]

Fluvoxamine in animal studies was found in higher concentrations in major organs (lung, liver, kidney) than in blood.[13] No unusual accumulation pattern was found. This finding is typical of the tricyclic antidepressants and other psychoactive drugs that are present in much higher concentrations in brain and other tissues than in plasma and relates to their high degree of lipophilicity.[14]

The clinical significance of extensive distribution is that extracorporeal methods of removing drug from the body (peritoneal and hemodialysis, hemoperfusion) may have only a minimal effect in lowering tissue drug concentrations. Fluvoxamine is remarkably safe in overdosage, and these treatments are considered unnecessary.[15] Extensive distribution also implies that replacement doses of fluvoxamine are not necessary in patients undergoing renal dialysis as a treatment for end-stage renal disease or other causes of severe renal impairment. Drug from tissues would be expected to rapidly re-equilibrate with plasma upon its removal from blood. However, dosage guidelines for these types of patients have not been specifically reported.

Volume of distribution. The volume of distribution of fluvoxamine has not been directly assessed with an intravenous drug study. Estimates from oral data place the value around 5 L/kg (Table 2). This is in keeping with a lipid soluble drug that is extensively distributed to tissues and is consistent with values found with other antidepressants.[2]

Protein binding. The distribution of drugs in the body is closely related to their degree of plasma protein and tissue binding. Plasma protein and tissue binding act in opposite directions to decrease or increase the volume of distribution of a drug. The greater the degree of tissue binding in relation to plasma binding, the larger the proportion of the total drug in the body that resides outside of the circulation and the greater the calculated volume of distribution. Binding to tissues is a pharmacokinetic parameter of considerable interest but one that is difficult to directly estimate and is complicated in its interpretation by nonspecific binding to tissues of little interest.

Knowledge of the degree of plasma protein binding is useful for its predictive value for the degree of hemodialysis and for the likelihood that a protein binding displacement mechanism may occur in drug-drug interactions. When drugs that are highly bound to the same plasma proteins (e.g., albumin, α_1-acid glycoprotein) are administered together, one drug may displace another when present in a sufficiently high enough concentration. This displacement can alter the clearance and pharmacologic effects of the displaced drug.

The tissue protein binding of fluvoxamine is presumably high given the estimated volume of distribution of 5 L/kg of the drug. The plasma protein binding of fluvoxamine has been reported from animal studies as 77%.[16] This is the lowest value of any of the SSRIs. This low degree of binding suggests that fluvoxamine is unlikely to participate in drug-drug interactions that are mediated by a plasma protein binding displacement mechanism.

Metabolism and Elimination

Fluvoxamine is the only SSRI lacking a chiral center. The importance of stereochemistry lies in the fact that many drugs are administered as a racemic mixture and, thus, have enantiomers that are identical in chemical structure but are often distinctly different in their pharmacokinetic and pharmacologic characteristics. Examples in clinical psychopharmacology include methylphenidate and fenfluramine. Quinidine, but not its stereoisomer quinine, is a potent CYP2D6 inhibitor. Paroxetine has two chiral centers but is administered as the pure transisomer. Fluoxetine and its metabolite norfluoxetine are racemates. R- and S-fluoxetine are almost equally potent as SSRIs, but S-norfluoxetine is almost 20 times more potent than R-norfluoxetine.[17] Fluvoxamine is without optical stereoisomers, and, thus, studies of its metabolism have not required concern for the implications of stereochemistry.

The primary methods by which drugs are eliminated from the body are by hepatic metabolism and/or renal excretion. When a drug is metabolized, it is considered to have been eliminated as it no longer exists in its original form even though a metabolite may have similar pharmacokinetic and pharmacologic characteristics. The concern at this point is with the further metabolism or renal elimination of any metabolite(s).

Metabolic pathways. Drugs may be biotransformed into metabolites that differ broadly in their pharmacologic characteristics from the parent drug. Metabolites may be pharmacologically active and contribute to the therapeutic effects of the parent drug. Metabolites may have toxic effects, or they may be devoid of meaningful pharmacologic activity. Psychoactive drugs provide examples of each of these situations. Desipramine, the demethylated metabolite of imipramine, contributes to the therapeutic effect of the parent tricyclic antidepressant. N-desmethylclozapine possibly contributes to the hematopoietic toxicity of clozapine, and, among the SSRIs, fluvoxamine and paroxetine produce metabolites that have essentially no pharmacologic effects.

Fluvoxamine is metabolized to at least 11 biotransformation products that have been recovered in urine after orally administered C^{14} radiolabeled fluvoxamine. Of the products that have been structurally identified, none have shown any significant pharmacologic activity.[17,18] A drug devoid of active metabolites has an advantage when relating observed pharmacologic effects to administered dose

or plasma drug concentration. For example, both fluoxetine and sertraline produce metabolites with activities on the serotonin transporter, although desmethylsertraline possesses much less activity in this regard than sertraline. Another implication of the presence of active metabolites is that they may also possess affinity for various P450 enzymes. This situation can complicate the ability to predict the potential of a drug to participate in drug-drug interactions. A lack of active metabolites also decreases the possibility of unexpected and delayed toxicity after overdosage.

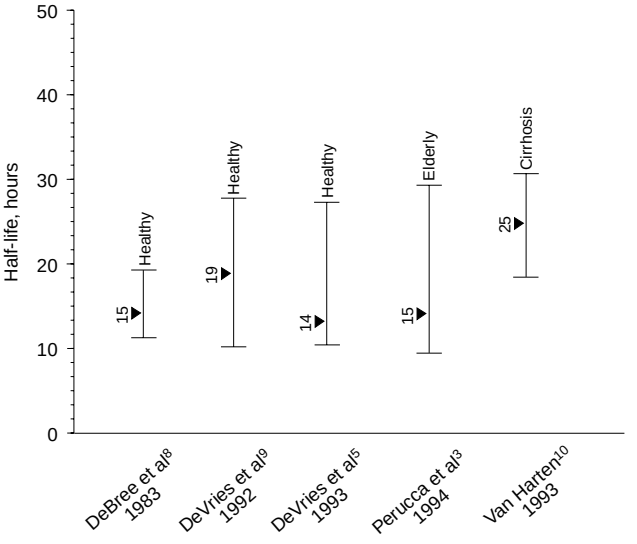
The specific enzymes responsible for the metabolism of fluvoxamine have not been identified. Fluvoxamine is a potent inhibitor of CYP1A2.[19] When one drug strongly inhibits the metabolism of another, there is the possibility that the same isozyme mediates the metabolism of both drugs. However, CY1A2 has not yet been shown to metabolize fluvoxamine. The strongest evidence for the involvement of CYP1A2 in the metabolism of fluvoxamine comes from a study in which the average steady-state plasma concentration of fluvoxamine in smokers was lower than in nonsmokers.[20] Smoking is known to induce the CYP1A2 enzyme and increase the metabolism of drugs eliminated by this enzyme.

Renal excretion. Less than 4% of an orally administered dose of C^{14} radiolabeled fluvoxamine was excreted in the urine in an unchanged form.[8] This high degree of metabolism suggests that renal impairment would have little overall effect on the pharmacokinetics of fluvoxamine.

Clearance. The estimation of clearance is essential to predict the steady-state concentration of drugs administered on a chronic basis. After ascending dosage studies, calculations of clearance estimates are also compared to test for linearity in the disposition of drugs. The magnitude of the systemic clearance is also informative as to the degree of hepatic extraction across the liver. Typical values of fluvoxamine clearance that have been reported along with steady-state drug plasma concentration are given in Table 2. The values reported for clearance are characteristic of a high extraction drug whose clearance is dependent on the degree of hepatic blood flow. Fluvoxamine may show nonlinearity in its clearance as the daily dose increases.[11] This results in higher plasma concentrations than would be predicted from single dose daily. As patients tolerate a wide range of steady-state concentrations apparently unrelated to the degree of side effects, this nonlinearity appears to have limited clinical significance.

Elimination half-life. This is perhaps the most clinically useful pharmacokinetic parameter for the practitioner to use in dosage regimen design.[21] Elimination half-life predicts the time necessary, upon continuous dosing, to achieve a steady-state concentration, the time to achieve a new steady state if the dosing rate is increased or decreased, and the time for drug to be eliminated from the body once dosing is discontinued. A time period equal to four to five half-lives defines each of the above situations.

Figure 1. Mean Elimination Half-Life and Range of Values Reported From Five Studies of Fluvoxamine.*



*Study subjects were healthy volunteers, elderly volunteers, or subjects with biopsy-proved hepatic cirrhosis.

After a single dose, the elimination half-life of fluvoxamine was about 15 to 22 hours.[3,10] These values predict that steady-state concentrations would occur upon continuous dosing in about 5 days. While this mean value of elimination half-life is helpful for the clinician to remember, it should be recognized that considerable variability may exist between patients in this pharmacokinetic parameter.

A comparison of fluvoxamine half-lives reported in five studies is shown in Figure 1.[4,5,8–10] It can be appreciated that a twofold to threefold variability is present in the range of half-lives reported, but the mean value is similar in these four studies of healthy volunteers and elderly subjects. Even though the half-life is prolonged in patients with hepatic cirrhosis, there is considerable overlap of subjects without liver disease. Thus, the expected time to reach a steady-state condition with fluvoxamine could be as short as 2 to 3 days or as long as 5 days. Dosage increases that are made in periods of time shorter than these will not have allowed the patient to accumulate the maximum amount of drug in their body for that particular dosage. Even though the therapeutic effects of SSRIs may not correlate directly with plasma concentration, it is prudent to wait at least four to five half-lives between dosage changes in order for a new steady-state equilibrium to occur. The half-life of fluvoxamine is generally thought not to vary substantially with its dosage, i.e., dose-dependent kinetics have not been apparent in previous studies.

The significance of the 15-hour average half-life of fluvoxamine is that it suggests the drug is appropriate for

once-daily dosing, yet it is not so long as to cause problems should adverse reactions occur and necessitate the discontinuance of the drug.

DISEASE STATES AND OTHER CONDITIONS AFFECTING DISPOSITION

Hepatic Impairment

The pharmacokinetics of fluvoxamine were investigated in 13 volunteers with biopsy proved cirrhosis.[10] After oral administration of 100 mg given in single doses, mean elimination half-life was 25 ± 11 hours (range, 13.3–41.3 hours), and the AUC was about 50% higher compared with data from healthy volunteers studied in a similar protocol.[8] The findings suggested that liver disease decreased hepatic clearance but that maximum plasma drug concentrations after a single dose were not unduly affected. A change in the dosage frequency would be appropriate in patients with liver disease and not necessarily a decrease in the size of the administered dose. Plasma protein binding was not measured, but the relatively low degree of binding (77%) (Table 2) suggests that this parameter might not change appreciably in cirrhotic patients.

The relevance of liver disease to the dosage regimen design of fluvoxamine is also necessarily concerned with the effects of the drug in patients who abuse alcohol. Depression is a frequent comorbid condition in alcoholics, and SSRIs may have some efficacy in reducing the propensity to drink in this population.[22] Thus, fluvoxamine may be prescribed in patients who are actively drinking or in patients who have alcohol-related liver disease. Fortunately, van Harten et al.[23] found that fluvoxamine did not interact with alcohol or potentiate alcohol-related impairment of cognitive function.

Renal Impairment

Data relating the disposition of fluvoxamine in patients with renal impairment have not been published. One review[3] has stated that plasma concentrations were similar in patients with impaired renal function taking fluvoxamine and healthy volunteers. The product labeling for fluvoxamine recommends a lower starting dosage in patients with renal disease.[11] This is reasonable advice as severe renal impairment will eventually affect hepatic function. Also, severe organ disease of any kind may alter the pharmacodynamic response to usual drug dosages. Thus, a lower starting dose will allow titration according to response and hopefully identify any patients with an unusual sensitivity to fluvoxamine.

Excretion in Breast Milk

The excretion of fluvoxamine in breast milk was reported in a patient who had been taking 200 mg of fluvoxamine daily for 2 weeks.[24] Breast milk contained 90 ng/mL as compared with a maternal plasma concentration of 310 ng/mL. Even though neonates may be hypothesized to be sensitive to psychoactive drug effects owing to the plasticity of their developing nervous system, a neonatal dose calculated on the basis of this breast milk concentration would be extremely low and suggests that the risk of potential toxicity from fluvoxamine excretion in breast milk is very small.

Age and Gender

Most studies of fluvoxamine pharmacokinetics have used healthy males. One study reported no difference in plasma fluvoxamine concentration according to gender.[25] De Vries et al.[5] found a mean fluvoxamine elimination half-life of 25 hours (range, 16–34 hours) in 13 elderly volunteers compared with a mean of 22 hours (range, 15–29 hours) in 6 young subjects. These data suggest that only a minimal prolongation of half-life could be expected in the elderly. Other data demonstrate that the clearance of fluvoxamine may be reduced by up to 50% in the elderly.[11] Thus, it is recommended that fluvoxamine dosing should be initiated cautiously in elderly patients. There are no data that suggest that initial fluvoxamine dosage should differ for men and women.

Tobacco Use

Tobacco use has been associated with lower plasma concentrations of tricyclic antidepressants compared with those of nonsmokers. This effect is probably due to induction of cytochrome P450 1A2, which is partly responsible for the demethylation of tricyclics. One study found lower plasma fluvoxamine concentrations in smokers compared with nonsmokers,[20] and the specific effect of tobacco use on fluvoxamine pharmacokinetics was confirmed in a formal study.[26]

Concomitant Drug Therapy

Fluvoxamine has been observed to increase the plasma concentration of concomitantly administered drugs, including theophylline,[27–30] haloperidol,[31] clozapine,[32–34] alprazolam,[20] diazepam,[35] and various tricyclic antidepressants.[36–40] A list of the in vivo reports of the drug interactions of fluvoxamine is given in Table 3. These interactions can be grouped according to the effects of fluvoxamine on specific cytochrome isozymes.

CYP1A2. Fluvoxamine is a potent inhibitor of CYP1A2 in vitro and is unique among the antidepressants in this ability.[19] Cytochrome 1A2 is the enzyme responsible for dealkylating theophylline, caffeine, and phenacetin. Other drugs believed to be metabolized by CYP1A2 include tacrine and clozapine. The tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) may be partially demethylated by this enzyme. The current recommendation is to reduce theophylline dosage to one third of the usual maintenance dose and monitor plasma theophylline concentration when beginning fluvoxamine.[9]

Table 3. Effects of Fluvoxamine on P450-Mediated Drug Metabolism in Vivo*

Drug	Subjects	Pharmacokinetic Observations	CYP
Imipramine[38]	V	↑ C_{max}, AUC, and $t_{1/2}$	1A2/2D6/3A4
Imipramine[37,39,40]	P	↑ Cpss	1A2/2D6/3A4
Desipramine[38]	V	No effect	2D6
Desipramine[37]	P	↑ Cpss	2D6
Desipramine[40]	P	No effect	2D6
Clomipramine[41]	P	↑ Cpss	2C19/2D6
Tricyclic antidepressants (various)[36,42]	P	↑ Cpss (reduced demethylation); No effect on hydroxylation	1A2/2C19/3A4 2D6
Haloperidol[31]	P	↑ Cpss	2D6
Clozapine[32–34]	P	↑ Cpss	1A2/2D6
Propranolol[11]	V	↑ C_{max} and AUC	1A2/2D6
Theophylline[27–30]	P	↑ Cpss	1A2
Carbamazepine[43–45]	P	↑ Cpss	3A4
Carbamazepine[46]	P	No effect on Cpss	3A4
Alprazolam[20]	V	↑ C_{max}, AUC, and $t_{1/2}$	3A4
Diazepam[35]	V	↑ AUC and $t_{1/2}$ ↑ AUC (N-desmethyl-diazepam)	2C19/3A4 2C19?
Warfarin[11,13]	…	↑ C_{max} and AUC	2C9
Methadone[47]	…	↑ Cpss	?

*Abbreviations: Cpss = steady state plasma concentration; C_{max} = maximal plasma concentration after a single dose; AUC = area under the plasma concentration versus time curve; V = healthy volunteers; P = patients; CYP = principal cytochrome P450 enzyme(s) involved in metabolic pathway relating to pharmacokinetic observations; ? = unknown or suspected.

Clozapine dosage should also be reduced in anticipation of an inhibition of clearance and rise in the plasma clozapine concentration.[32–34] Propranolol is partially metabolized by CYP1A2. If propranolol is to be coadministered with fluvoxamine, a greater intensity of β-blockade might be expected.[11] Hypotension and bradycardia are possible, and careful dosage titration should be performed when adding fluvoxamine to a drug regimen that includes propranolol.

CYP2C. To a lesser extent than its effects on CYP1A2, fluvoxamine can inhibit the metabolism of substrates for CYP2C.[13,35] This is one of the enzymes that mediates the demethylation of tricyclic antidepressants. Elevations of tertiary amine tricyclic plasma concentration have been reported when fluvoxamine was combined in therapy (Table 3).

CYP2C9 metabolizes warfarin, and an increased warfarin concentration has been reported in combination with fluvoxamine.[11] When these drugs are to be used together, patients should have their prothrombin time monitored frequently and their anticoagulant dose adjusted accordingly to maintain coagulation status in the desired state.

CYP3A4. Fluvoxamine has affinity for CYP3A4.[20,43–45] The major evidence for the effects of fluvoxamine on CYP3A4 substrates comes from a pharmacokinetic study in which fluvoxamine increased plasma alprazolam.[20] The elimination half-life of alprazolam increased from 20 hours to 34 hours after fluvoxamine coadministration. If fluvoxamine is to be coadministered with alprazolam, the initial alprazolam dosage should be reduced by 50% or more. As fluvoxamine has also been shown to prolong the elimination of diazepam and its major active metabolite desmethyldiazepam,[35] a similar reduction in dosage would be appropriate for this benzodiazepine or the drugs should not be used together.

Other precautions applicable to CYP3A4 substrates apply to combination therapy with terfenadine and astemizole. These antihistamines are metabolized by CYP3A4. Blockade of their metabolism by ketoconazole has resulted in increased plasma concentrations of parent drug and QT prolongation and torsade de pointes-type ventricular tachycardia. Thus, the evidence for the effects of fluvoxamine on CYP3A4 suggests it should be avoided in patients who must be treated with these antihistamines.

CYP2D6. This enzyme is responsible for metabolizing a variety of therapeutically important drugs, including some antipsychotics, codeine, some β-blockers, and antiarrhythmics, and mediates the hydroxylation pathway of tricyclic elimination. Fluvoxamine is a relatively weak inhibitor of CYP2D6, and no adjustment of dosage is necessary when combined with substrates for this isozyme.

CORRELATIONS WITH CLINICAL EFFECTS

Effective Concentrations in Patients

Plasma fluvoxamine concentration has been correlated to clinical effects in several studies.[25,48–51] A broad range of concentrations are found in patients receiving therapeutic doses, generally between 20 and 500 ng/mL. One study found that most responders had a steady-state concentration in a narrow range of 160 to 220 ng/mL.[51] However, several studies[25,48,49] report a wide variability in the range of plasma concentrations among responders and no correlation with dosage. The range of plasma concentrations expected from usual doses is given in Table 2. Kasper et al.[7] found that concentrations of fluvoxamine higher

than 131 ng/mL in depressed patients were associated with more sleep disturbances, but no difference was found in plasma drug concentrations between responders and nonresponders. The available data do not suggest benefits from routine monitoring of plasma fluvoxamine concentration.

CONCLUSION

The clinical pharmacokinetics of fluvoxamine are reasonably well defined. The drug is well absorbed after oral administration, although slowly, but is not affected by the coadministration of food. Fluvoxamine, like all antidepressants, is widely distributed in the body. It has an elimination half-life averaging 15 hours and produces no active metabolites. Initial dosage should be reduced in patients with advanced liver disease and in the elderly.

Fluvoxamine has potent effects on the CYP1A2 isozyme and should be dosed with caution in patients receiving substrates metabolized by this enzyme. The list includes theophylline and clozapine as drugs displaying a relatively narrow therapeutic range. Less potent inhibition has been demonstrated with drugs metabolized by CYP2C9 and CYP3A4. Combining therapy with tertiary amine tricyclics (imipramine, clomipramine, amitriptyline), alprazolam, carbamazepine, terfenadine, and astemizole should be approached with caution for possible interactions. Only limited data are available on the value of monitoring plasma fluvoxamine concentrations, and this practice is not yet justified. Fluvoxamine is tolerated very well across a broad range of plasma concentrations, and toxicity from elevated plasma drug concentration has not been shown to be of concern. Overall, the pharmacokinetic profile of fluvoxamine is reasonably well defined for most situations.

Drug names: alprazolam (Xanax), amitriptyline (Limbitrol), astemizole (Hismanal), carbamazepine (Tegretol and others), clomipramine (Anafranil), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), imipramine (Tofranil and others), ketoconazole (Nizoral), methylphenidate (Ritalin), paroxetine (Paxil), phenacetin (Phensal), propranolol (Inderal and others), quinidine (Duraquin and others), sertraline (Zoloft), terfenadine (Seldane), theophylline (Constant-T and others), warfarin (Coumadin and others).

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