Psychotropic Medications and Cytochrome P450 2D6: Pharmacokinetic Considerations in the Elderly

Richard W Shulman, MD, FRCPC, Vural Özdemir, MD, MSc

Background: The genetically polymorphic cytochrome P450 2D6 isozyme (CYP2D6) is responsible for the metabolism of numerous psychotropic medications pertinent to the practice of geriatric psychiatry. Optimal use of psychotropics in the elderly requires a thorough understanding of the determinants of marked variability in plasma concentrations. This review article will focus on basic pharmacokinetic considerations for elderly patients when psychotropics metabolized by CYP2D6, such as nortriptyline and desipramine, are prescribed.

Method: A MEDLINE search was conducted using the subject headings “cytochrome P450,” “pharmacokinetics,” and “psychotropics.” Relevant articles from bibliographies were also collected.

Results: CYP2D6 activity does not change with age. Approximately 5% to 10% of whites are poor metabolizers for CYP2D6 and are at risk for drug toxicity. Among Asians, although the prevalence of poor metabolizers is only 1%, the distribution of CYP2D6 activity in extensive metabolizers is shifted toward lower values relative to whites. CYP2D6 activity may be impaired by inhibitors such as paroxetine and fluoxetine. Inhibition of CYP2D6 activity may result in nonlinear plasma drug concentration kinetics, as well as kinetic drug interactions when other drugs metabolized by CYP2D6 are coadministered. Among extensive metabolizers, there is considerable interindividual variation in CYP2D6 activity. Significant correlations have been reported between individual CYP2D6 activity and plasma concentrations of nortriptyline and desipramine.

Conclusion: Clinical measurement of CYP2D6 activity may potentially assist in prediction of doses required to achieve therapeutic plasma concentrations of psychotropics metabolized by CYP2D6 in individual patients. Although CYP2D6 activity does not change with age, the pharmacokinetics of psychotropics metabolized by CYP2D6 may change because of age-associated changes in hepatic blood flow, volume of distribution, and renal elimination of metabolites.

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Key Words: cytochrome P450 2D6, genetic polymorphism, pharmacokinetics, clearance, metabolism, psychotropics, elderly, nortriptyline, desipramine

The elderly are the fastest-growing segment of the North American population (1). Optimal use of psychotropics in the elderly requires an understanding of the factors responsible for interindividual variability in plasma drug concentra-

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1 Assistant Professor, Department of Psychiatry, University of Toronto, Toronto, Ontario; Psychiatrist, Division of Geriatric Psychiatry and Psychopharmacology Research Program, Sunnybrook Health Science Centre, North York, Ontario.

2 PhD Candidate, Department of Pharmacology, University of Toronto, Toronto, Ontario; Fellow, Department of Psychiatry and Psychopharmacology Research Program, Sunnybrook Health Science Centre, North York, Ontario.

Address for correspondence: Dr RW Shulman, Department of Psychiatry, Sunnybrook Health Science Centre, 2075 Bayview Avenue, Room FG20, North York, ON M4N 3M5

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The CYP enzymes located in the endoplasmic reticulum of cells are involved in the oxidative metabolism of medicaments, as well as precarcinogens and carcinogens (14,15). The nomenclature for grouping the different CYP enzymes is based on the degree of homology in their amino acid sequences (16). The CYP enzymes are grouped into families, designated by an arabic number, that have at least 40% amino acid sequence homology (for example, CYP2). They are further divided into subfamilies (designated by an upper case letter), that have, in mammals, at least 55% amino acid sequence homology (for example, CYP2D). Within each subfamily, the individual isozymes are designated by an arabic number (for example, CYP2D6).

CYP2D6 is of particular interest to geriatric psychiatrists because it is involved in the metabolism of numerous psychotropics pertinent to the practice of geriatric psychiatry: desipramine, nortriptyline, paroxetine, fluoxetine, trazodone, venlafaxine, tiapride, disopyramide, imipramine, and haloperidol, among others (17,18). Drugs may be metabolized by more than one CYP enzyme. For example, amitriptyline, clomipramine, and imipramine are tertiary amine tricyclic antidepressants (TCAs) metabolized by CYP2D6 in addition to other CYP enzymes (17). In contrast, the secondary amine TCAs, nortriptyline and desipramine, are primarily metabolized by CYP2D6 (19–21). This review article will focus on basic pharmacokinetic principles and clinical considerations for elderly patients being prescribed psychotropics metabolized by CYP2D6. Nortriptyline and desipramine will be used as examples of how knowledge of CYP2D6 activity may potentially assist clinicians to predict individualized dosages.

Basic Pharmacokinetic Principles

Clearance

The rate of drug elimination from the body can best be quantified by the concept of clearance (Cl). Clearance is described as the volume of blood, serum, or plasma from which a substance is completely removed per unit of time (3). Hepatic drug clearance depends on the rate of hepatic blood flow, the intrinsic affinity of hepatic enzyme(s) for the drug, and the enzyme catalytic activity. Plasma drug concentrations may follow linear or nonlinear kinetics. In linear kinetics, changes in drug concentration are proportional to changes in dose. In nonlinear kinetics, changes in drug concentration are disproportional to changes in dose, for example, enzyme activity may be saturated or inhibited.

Volume of Distribution

Volume of distribution (apparent) (Vd) is an index of how widely a drug is distributed throughout the body and is a function of total body fat for drugs that are lipophilic (for example, all psychotropics except for lithium). For most psychotropics, therefore, Vd is often very large and plasma concentrations are small relative to the total amount of the drug in the body. Vd exhibits significant interindividual variation because of individual differences in percentage body fat. This variability also reflects gender-associated differences because females have a higher fraction of body weight comprised of adipose tissue (7). As most people age, body water and lean muscle mass decrease while total body fat tends to increase, even if total body weight remains relatively constant (22,23). As a result, Vd of lipid-soluble drugs is larger in the elderly, indicating that drugs are distributed more extensively in the peripheral body tissues (4,7).

Elimination Half-Life

Elimination half-life (t1/2) can be expressed as the time required to eliminate 50% of the drug from the body. A practical principle (7) to remember is:

$$t_{1/2} = \frac{Vd}{Cl}$$

Since t1/2 is directly proportional to Vd, given equal Cl, a larger Vd results in a longer time period to eliminate the drug. This is one of the major reasons for longer t1/2 of drugs used in the elderly. Conversely, since t1/2 is inversely proportional to Cl, given equal Vd, reduced Cl will also result in longer time periods to eliminate the drug. Hepatic Cl can be decreased by reductions in hepatic blood flow or in enzyme activity. In the elderly, hepatic blood flow is commonly impaired by hypotension or by impairment in left ventricular function due to disease (heart failure) or drugs (B-blockers). Decreased hepatic enzyme functioning may occur by medications saturating or inhibiting enzyme activity (discussed later), or in liver diseases.

Steady-State Plasma Concentration

Cl is also a major determinant of steady-state plasma concentration (Css) (7). During chronic dosing:

$$C_{ss} = \frac{\text{Dosing rate}}{Cl}$$

Reduced Cl, therefore, also will result in higher Css unless the dosing rate is decreased.

Metabolism

After oral administration, most psychotropics are absorbed in the small intestine and reach the liver by means of portal circulation. In the liver, they are metabolized to a certain extent prior to entering the systemic circulation. This is called the first-pass effect, which depends on hepatic Cl. Drug metabolism is divided into 2 phases. Phase 1 reactions consist mainly of oxidation, reduction, and hydrolysis, which introduce or unmask a functional group (for example, a hydroxyl moiety). Phase 2 reactions consist of conjugation (for example, glucuronidation) of the functional group de-
derived from phase 1 reactions, producing a more polar metabolite. The increase in hydrophilicity facilitates elimination of metabolites by the kidney or in the feces (24).

Measurement of CYP2D6 Activity In Vivo

CYP2D6 activity can be determined clinically by in vivo drug probes including dextromethorphan, debrisoquine, and sparteine. This is a simple and safe procedure that involves the administration of a single oral dose of the probe drug (usually at bedtime), with subsequent collection of urine for a period of 8 hours. The urine samples are analyzed for the concentrations of the probe drug and its metabolites produced by CYP2D6. The metabolic ratio of the concentration of probe drug and its metabolite(s) serves as an index of CYP2D6 activity in vivo. Clinical screening for CYP2D6 activity can also be performed by genotyping for the CYP2D6 alleles. Poor metabolizers are homozygous for mutated alleles, which result in a nonfunctional CYP2D6 isozyme. Extensive metabolizers are either homozygous for the wild-type allele, or heterozygous for the wild-type and a mutated allele (21).

Genetic Variability in CYP2D6 Activity

The expression of CYP2D6 activity displays significant genetic and interethnic variability (10,25). Approximately 5% to 10% of whites are poor metabolizers for CYP2D6 (25–29) and lack the functional CYP2D6 enzyme (30). The rest of the population are considered as extensive metabolizers. The activity of CYP2D6 is practically noninducible by environmental factors (31) and does not change with age (32). For psychotropics metabolized by CYP2D6, the clinically relevant point is that plasma concentrations are higher in poor metabolizers compared with extensive metabolizers (9) and may result in drug toxicity (33). In addition to this categorical classification dividing the population into 2 distinct groups, it is important to recognize that CYP2D6 activity varies more than a hundredfold among extensive metabolizers (25). Variability in the extensive metabolizer group, therefore, may also have clinical importance. A certain subset of extensive metabolizers are ultrarapid metabolizers and present with a very high clearance of CYP2D6 substrates (34–37), resulting in low plasma concentrations. Clinically, these individuals may be misdiagnosed as being noncompliant or resistant to psychotropic drug treatment (38). Ethnic variations also exist. Among Asians, although the prevalence of poor metabolizers is only 1%, the distribution of CYP2D6 activity in extensive metabolizers is shifted towards lower values relative to whites (25), which may lead to higher plasma concentrations of CYP2D6 substrates, as demonstrated with haloperidol (39). Genetic interindividual variability in CYP2D6 activity accounts considerably for the marked interindividual variability in pharmacokinetics of drugs metabolized principally by CYP2D6, as demonstrated in kinetic studies of nortriptyline and desipramine (11–13,18,38,40–42).

Individualized Dose Prediction for Desipramine and Nortriptyline

The secondary amine TCAs, nortriptyline and desipramine, are recommended over the tertiary amine TCAs (amitriptyline, imipramine, and clomipramine) for the treatment of depression in the elderly because they are less anticholinergic and cause fewer side effects (43–45). Nortriptyline is the most frequently studied antidepressant in the elderly (46) and is still used as a first-line treatment for major depression in this age group (47). A therapeutic plasma concentration threshold of 115 ng/mL (432 nmol/L) has been shown for desipramine in adults (48). This finding has been replicated in the elderly (49,50) but not in those over age 75 who may show resistance to treatment (51). For nortriptyline, a significant curvilinear relationship between therapeutic response and nortriptyline plasma concentrations ranging from 58 to 148 ng/mL (220 to 562 nmol/L) has been shown in younger patients (48). A 1994 review of 22 studies of nortriptyline in the elderly (of which 11 were outcome studies) involving an estimated 300 patients concluded that nortriptyline has a therapeutic window in the same plasma-concentration range as that for younger adults (46). Although a consensus on the applicability of these data for clinical practice is lacking (52), dosing nortriptyline and desipramine in the elderly to achieve therapeutic plasma concentrations remains problematic because specific dosing recommendations without the use of blood monitoring have not been derived.

Prediction of the required dose to achieve a therapeutic concentration prior to commencing treatment could possibly be determined by knowledge of CYP2D6 activity. A significant correlation between the C ss of desipramine and CYP2D6 activity has been shown (r = 0.92, P < 0.01, n = 10) (20). This suggests that measuring CYP2D6 activity may assist in prediction of the C ss of desipramine for a given dose. This approach may also be applicable for nortriptyline. In a study of depressed patients treated with nortriptyline, there was a significant correlation between the plasma concentration of nortriptyline (per unit dose) and CYP2D6 activity (r = 0.77, P < 0.01, n = 20) (41). This correlation has been replicated in elderly subjects. In nortriptyline-compliant geriatric patients previously assessed for CYP2D6 activity, the therapeutic doses of nortriptyline needed to achieve a concentration of 80 to 120 ng/mL (304 to 456 nmol/L) were significantly correlated with CYP2D6 activity (r = 0.73, P < 0.001, n = 20) (53). These studies provide preliminary evidence that measuring CYP2D6 activity may help predict nortriptyline and desipramine dose requirements in elderly patients.
Changes in Kinetics of CYP2D6 Substrates in the Elderly

In geriatric psychiatry, it is a widely held notion that psychotropic drug metabolism decreases in the elderly. This stems in part from findings of increased plasma concentrations of tertiary amine TCAs and oxidatively metabolized benzodiazepines in the elderly (54–59). However, in vitro and in vivo studies in humans do not uniformly support an age-associated decline in hepatic drug metabolism (32,60–63). The pharmacokinetics of nortriptyline and desipramine in healthy elderly controls and elderly depressed patients without physical illness have been found to be similar to those in younger patients, suggesting that no changes in dosing are required because of age alone (42). Nevertheless, clinical studies have shown that those over the age of 75, the “old-old,” may have markedly different plasma levels for given doses than patients in younger age groups (64). A survey of the literature reporting on comparative plasma level-to-dosage ratios (L:D) for nortriptyline indicates L:D ratios of 0.96:1.26 in adult patients, whereas the ratio increases after age 65 to 1.83:2.11, with the sharpest upward change taking place after 69 years of age (65). Since CYP2D6 activity does not appear to change with age (32), age-associated increases in the plasma concentration of psychotropics metabolized predominantly by CYP2D6 are more likely to be attributable to reduced hepatic Cl due to reduction in hepatic blood flow or other medications inhibiting CYP2D6 activity. In addition to reduced Cl, increased elimination half-lives are also possible as a result of increased Vd due to the increased percentage of body fat in elderly people.

Elimination of Secondary Amine TCA Metabolites in the Elderly

Nortriptyline and desipramine are principally metabolized by CYP2D6 by means of ring hydroxylation to 10-hydroxynortriptyline and 2-hydroxydesipramine, respectively (20,66). Reduced elimination of these polar metabolites is expected because of age-associated decline in renal function (67–70). Clinically, these metabolites are not usually measured because the ratio of the metabolites to their parent compounds is relatively constant at usual therapeutic concentrations; however, aging could change the expected relationship between the measured parent drug concentration and its active metabolites. Clinical consequences for most patients are probably minimal, as suggested by the similar rates of efficacy for nortriptyline in young and old (46), but may be important for certain patients. For example, ultrarapid metabolism has been reported to lead to lack of response, even when the dose is increased to allow for nortriptyline levels within the therapeutic window (38). This nonresponse may be due to the high concentration of metabolites that accumulate and perhaps somehow interfere with nortriptyline action. Accumulation of 2-hydroxydesipramine may also explain the reduced efficacy of desipramine reported in those over age 75 (51).

Environmental Factors Responsible for Variation in CYP2D6 Activity

Although CYP2D6 activity does not appear to change with aging (32), it may still be impaired in the elderly because of inhibition by medications such as the selective serotonin reuptake inhibitors (SSRIs) (17,18,71–75). Overall, paroxetine and fluoxetine are potent inhibitors of CYP2D6. Sertraline may be an inhibitor of CYP2D6 at high doses (76), although another study did not confirm this (77). Fluvoxamine and venlafaxine do not inhibit CYP2D6 significantly (78,79). Norfluoxetine, the active metabolite of fluoxetine, reaches a sufficient concentration under routine clinical conditions to cause CYP2D6 inhibition in addition to that of the parent compound. Because of norfluoxetine’s extended half-life (1 to 2 weeks), the risk of CYP2D6 inhibition will persist for weeks (80). Clinical considerations would be to use low doses when prescribing CYP2D6 substrates in patients taking CYP2D6 inhibitors. Therapeutic drug monitoring, if available, may help prevent unintentional toxicity. Since TCA toxicity can be life-threatening, SSRI and secondary amine TCA combinations are not commonly used (17) and are probably best avoided. Knowledge of potential kinetic interactions are also of practical importance when switching to a secondary amine TCA from paroxetine, fluoxetine, and perhaps sertraline (at doses equal to or above 150 mg/day). Doses of nortriptyline or desipramine should be kept low until the inhibitor is washed out—about 5 days for paroxetine but up to 5 to 8 weeks in the elderly for norfluoxetine (81).

Neuroleptic Substrates of CYP2D6

Neuroleptics metabolized by CYP2D6 include perphenazine, haloperidol, zuclopenthixol, risperidone, and thioridazine (9,17,82). Genetic deficiency or significant inhibition of CYP2D6 activity by the potent inhibitors paroxetine and fluoxetine may result in neuroleptic toxicity (83). Haloperidol, perphenazine, and thioridazine are also potent inhibitors of CYP2D6 that may lead to autoinhibition of their own metabolism, resulting in nonlinear kinetics and potential side effects during continued treatment (33).

Conclusion

In summary, both genetic and environmental factors contribute to interindividual variability in Cl of psychotropics metabolized by CYP2D6. In the elderly, there is no direct evidence for decreased CYP2D6 function. Other factors, however, such as illnesses that result in changes in hepatic blood flow or concomitant medications inhibiting enzyme activity, may reduce hepatic Cl of psychotropics metabolized by CYP2D6. Longer elimination half-lives may also be
expected because of the increased Vd, which is a result of the increased percentage body fat. In general, elderly patients require lower doses of medications to achieve therapeutic plasma concentrations, except for those who are rapid metabolizers. Clinicians should remember that 5% to 10% of whites are poor metabolizers of CYP2D6 in whom even low doses of CYP2D6 substrates may not be tolerated. CYP2D6 activity can be easily measured and has been shown to correlate significantly with plasma nortriptyline and desipramine concentrations. The available data provide a basis for future clinical assessment of the value of measuring CYP2D6 activity to predict the doses of nortriptyline and desipramine required to achieve therapeutic concentrations.

Clinical Implications

- Both genetic and environmental factors contribute to the marked interindividual variability in CYP2D6 activity.
- CYP2D6 activity does not change with age.
- Associations between CYP2D6 activity and plasma concentrations of the secondary amine TCA's nortriptyline and desipramine may provide a basis for future clinical assessment of the value of measuring CYP2D6 activity to predict dosages required to achieve therapeutic concentrations safely.

Limitations

- This paper does not review all the pharmacokinetic studies of psychotropics metabolized by CYP2D6 in the elderly.
- It is not a review of drug interaction studies with CYP2D6 inhibitors.
- It does not address pharmacodynamic differences in the elderly.

References

Résumé

Toile de fond: Le cytochrome P450-isozyme 2D6 (CYP2D6) génétiquement polymorphe est responsable du métabolisme de nombreux médicaments psychotropes pertinents à l’exercice de la psychiatrie gériatique. Le recours optimal aux psychotropes chez les personnes âgées exige une compréhension approfondie des déterminants d’une variabilité importante des concentrations plasmatiques. Cet article de synthèse est axé sur des considérations pharmacocinétiques fondamentales relatives aux patients âgés quand on leur prescrit des psychotropes métabolisés par le CYP2D6, comme la nortriptyline et la désipramine.


Résultats: L’activité du CYP2D6 ne varie pas en fonction de l’âge. Environ 5 à 10 % des sujets de race blanche métabolisent mal le CYP2D6 et présentent un risque de toxicité médicamenteuse. Chez les Asiatiques, bien que la prévalence d’un métabolisme faible ne soit que de 1 %, la répartition de l’activité du CYP2D6 chez les sujets ayant un métabolisme important s’est déplacé vers des valeurs moins élevées par rapport aux sujets de race blanche. L’activité du CYP2D6 peut être altérée par des inhibiteurs, comme la paroxétine et la fluoxétine. L’inhibition de l’activité du CYP2D6 peut se traduire par une courte pharmacocinétique non linéaire des concentrations plasmatiques, ainsi que par des interactions médicamenteuses d’ordre cinétique lorsqu’on administre simultanément d’autres médicaments métabolisés par le CYP2D6. Chez les sujets dont le métabolisme est important, on constate une variation interindividuelle considérable de l’activité du CYP2D6. Des corrélations significatives ont été signalées entre l’activité individuelle du CYP2D6 et les concentrations plasmatiques de nortriptyline et de désipramine.

Conclusion: La mesure clinique de l’activité du CYP2D6 pourrait éventuellement faciliter la préservation des doses nécessaires pour atteindre les concentrations plasmatiques thérapeutiques des psychotropes métabolisés par le CYP2D6 chez certains patients. Bien que l’activité du CYP2D6 ne varie pas en fonction de l’âge, la pharmacocinétique des psychotropes métabolisés par le CYP2D6 peut changer en raison de modifications de la circulation hépatique, du volume de distribution et de l’élimination rénale des métabolites liées à l’âge.