Cytochrome P450 2D6 Polymorphism and Its Impact on Decision-Making in Psychopharmacotherapy: Finding the Right Way in an Ultrarapid Metabolizing Patient

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The cytochrome P450 (CYP) superfamily represents the most important phase I drug metabolizing enzyme system. Genetic mutations play an important role in the activity especially of CYP2D6. Genetic polymorphisms within CYPs affect the metabolism of drugs as substrates for the particular enzymes, resulting in variations in plasma levels of the drugs, differences in drug response, or altered risk for adverse effects.[1] Most individuals have 2 copies of *CYP2D6,* and their genotype is defined by these 2 alleles. It is also possible to have 2 or more copies of *CYP2D6* on a single chromosome: as many as 13 copies have been reported to exist in 1 extraordinary patient.[2] Theoretically, thousands of *CYP2D6* genotypes can result from the various possible pairings, but traditionally CYP2D6 activity is classified in 4 broad clinical CYP2D6 metabolic phenotypes: poor metabolizers, extensive metabolizers, intermediate metabolizers, and ultrarapid metabolizers. The latter phenotype leads to problems in finding adequate therapeutic doses due to an inability to achieve therapeutic drug concentrations.

We report the case of a 55-year-old woman from Turkey, where the prevalence of CYP2D6 ultrarapid metabolizers is 10%.[3] She neither reached therapeutic drug concentrations of different drugs (metabolized via CYP1A2, CYP2D6, and CYP3A4) "natively" nor reached therapeutic plasma levels by pharmacologic blocking of CYP1A2 or CYP2D6. This led to the suggestion of a multiple ultrarapid metabolizer status, narrowing the psychiatrist's ability to bring about clinical remission.

Case report. Ms A, a 55-year-old woman suffering from a severe depressive episode with psychotic symptoms (*ICD-10*: F32.3), presented for initial treatment in early 2010 as an inpatient in a specialized ward for affective disorders at the Department of Psychiatry, Psychotherapy and Psychosomatics at the University Hospital of RWTH Aachen University, Aachen, Germany. Clinical examination, extensive blood testing, electroencephalography, and computed tomography of the brain showed no evidence of an organic or symptomatic mental disorder.

Because of her depressive symptoms, Ms A was started on treatment with duloxetine, and doses were increased over a period of 42 days to a maximum of 120 mg/d. (A history of the administered drugs, the daily doses, and the duration of treatment is illustrated in Figure 1.) Therapeutic drug monitoring of duloxetine (120 mg/d) at trough levels under steady-state conditions revealed maximal plasma levels of 21 ng/mL (reference range, 30–120 ng/mL[4]). Plasma levels were quantified as trough levels using high-performance liquid chromatography with spectrophotometric detection and column switching as described elsewhere.[5] Additional administration of fluvoxamine (50 mg/d) starting at week 8 to selectively block CYP1A2 in combination with 60 mg/d of duloxetine led neither to higher plasma levels of duloxetine[6] nor to a sufficient clinical response. Lithium, which is excreted renally, was added for augmentative reasons, and although therapeutic levels were easily reached (0.95 mmol/L), clinical response was lacking.

Augmentation with 20 mg/d of aripiprazole for more than 8 weeks (metabolized via CYP2D6 and CYP3A4) and with 300 mg/d of quetiapine for 8 weeks (metabolized mainly via CYP3A4, but also via CYP2D6) did not lead to therapeutic drug concentrations at any time. Plasma quetiapine levels with a daily dosage of 300 mg reached a maximum of 18 ng/mL quetiapine at trough levels (reference range, 100–500 ng/mL[4]), while plasma aripiprazole levels at doses of 20 mg/d were 51 ng/mL under steady-state conditions (reference range, 150–500 ng/mL[4]).

Therefore, the therapeutic approach was changed to an augmentative strategy using venlafaxine (metabolized by CYP2D6) and paroxetine, which is known to substantially block CYP2D6.[7] Venlafaxine dosage was increased up to 750 mg/d (maximum US Food and Drug Administration–approved dose: 375 mg/d), and the paroxetine dose was increased up to 80 mg/d (maximum approved dose: 60 mg/d). This combination strategy (venlafaxine 750 mg, paroxetine 80 mg) was maintained for 3 weeks until it was terminated due to lack of clinical response and not because of adverse reactions.

Therapeutic drug monitoring revealed plasma levels not only far below therapeutic efficacy according to well-established reference ranges (Figure 2) but also below dose-related reference ranges.[8] The latter implies a correlation between the quantity of the administered drug and the expected plasma level depending on drug metabolism and clearance. Dose-related reference ranges shift the focus toward individual abnormalities such as drug-drug interactions, gene polymorphisms that give rise to poor/ultrarapid metabolizers, altered function of the excretory organs (liver and kidneys) caused by age or disease, and compliance problems. According to Haen et al,[8] the reference range is calculated as $C_u = D \times F_u$ for the upper (*u*) threshold of the dose-related reference range and as $C_l = D \times F_l$ for the lower (*l*) threshold. *C* represents the estimated plasma concentration of the drug, *D* represents the daily maintenance dose, and *F* (or "factor") represents an approach accounting for bioavailability, dose interval, and total clearance of the drug as a basis for calculating reference doses.[8] Dose-related ranges are therefore obtained by multiplying *F* by the dose. For venlafaxine, the dose-related reference range is expected to be between the upper threshold of $C_u = D_{VEN} \times 0.93$ ng/mL and the lower threshold of $C_l = D_{VEN} \times 0.45$ ng/mL, and *O*-desmethylvenlafaxine is estimated to be between $C_u = D_{VEN} \times 2.20$ ng/mL and $C_l = D_{VEN} \times 1.12$ ng/mL.

Figure 1. Timeline of the Daily Doses and the Duration of the Treatment of the Administered Drugs

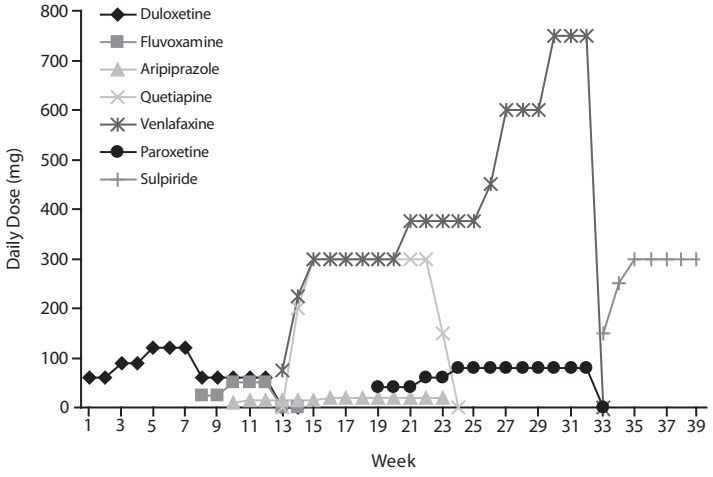
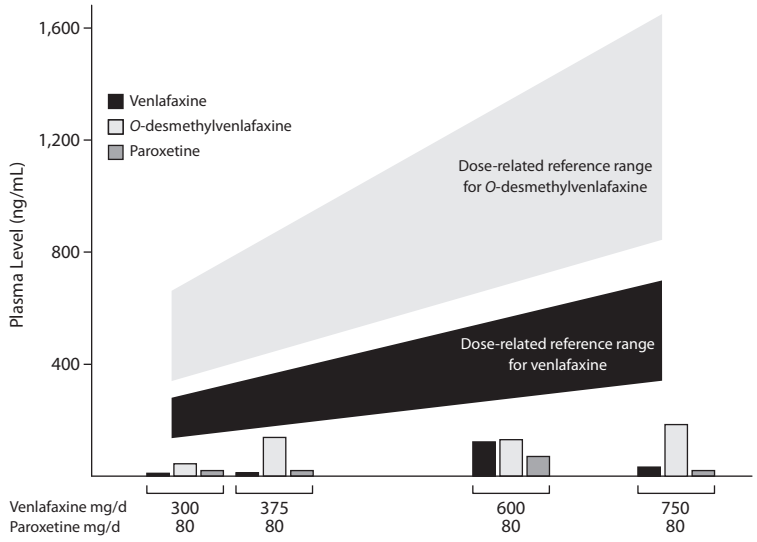
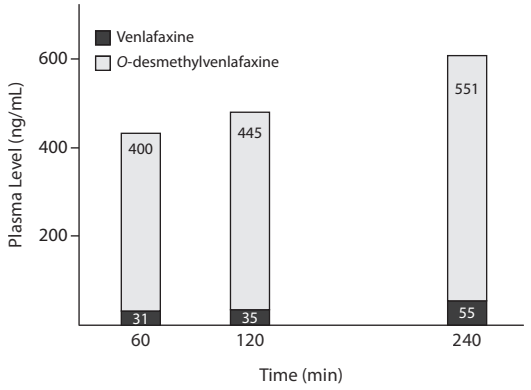


Figure 2. Plasma Levels and Dose-Related Reference Ranges at Trough Levels[a]



[a]Dose-related reference ranges calculated according to Haen et al.[8]

Figure 3. Venlafaxine and *O*-Desmethylvenlafaxine Levels Measured Shortly After Intake at Peak Levels to Exclude a Disturbance of Intestinal Absorption



Although CYP2D6 was blocked by 80 mg/d of paroxetine (week 1 plasma level: < 20 ng/mL, week 2 plasma level: 71 ng/mL), plasma levels of venlafaxine and *O*-desmethylvenlafaxine were far below the reference range. At a dosage of 750 mg/d of venlafaxine, the highest measured plasma level for venlafaxine was 31 ng/mL and for *O*-desmethylvenlafaxine, 183 ng/mL (reference range, 100–400 ng/mL[4]; dose-related reference ranges at 750 mg/d, 337.5–697.5 ng/mL for venlafaxine and 840–1,650 ng/mL for *O*-desmethylvenlafaxine). To exclude the possibility of a disturbance of intestinal absorption, we measured venlafaxine and *O*-desmethylvenlafaxine peak concentrations 60, 120, and 240 minutes after intake. Analysis of plasma levels revealed drug levels up to 606 ng/mL (55 ng/mL venlafaxine, 551 ng/mL *O*-desmethylvenlafaxine), indicating a sufficient intestinal absorption (Figure 3).

Genotyping of the patient revealed an ultrarapid metabolizer status for CYP2D6 with identification of the *CYP2D6*2XN* allele with at least more than 1 copy of *2 variant in chromosome 22. For *CYP2C19*, the allele *CYP2C19*1* was identified, reflecting normal enzyme activity.

Different metabolic pathways (CYP1A2: duloxetine, fluvoxamine; CYP2D6: venlafaxine, paroxetine, aripiprazole; CYP3A4: aripiprazole, quetiapine) were addressed and blocked, but none of the hepatically metabolized drugs reached therapeutic blood levels, measured as trough levels. As remission failed—despite blocking the metabolic pathways of the liver—the treatment regimen was switched to the benzamide sulpiride (for which the available data indicate antidepressant properties[9]), bypassing liver function, so that finally a partial remission was achieved although plasma levels with daily doses of sulpiride 300 mg were still comparably low (53 ng/mL; reference range, 200–1,000 ng/mL[4]).

The present case illustrates that therapeutic drug monitoring is an important tool to use in the development of antidepressant treatment strategies because it supports decision making on the basis of pharmacokinetic and pharmacogenetic considerations. In this case of a 55-year-old female Turkish inpatient, therapeutic drug monitoring revealed insufficient plasma levels of various psychotropic drugs that are metabolized via the cytochrome P450 superfamily, in particular CYP1A2, CYP2D6, and CYP3A4. Although all of the drugs were administered for an adequate time period and in appropriate doses, sufficient plasma levels were never observed. Even a pharmacologic blockade of CYP1A2 and CYP2D6 did not lead to higher plasma levels of drugs that are mainly metabolized via these 2 subtypes of cytochrome P450 enzymes. Therefore, from a clinical point of view, if the *O*-desmethylvenlafaxine/venlafaxine ratio is interpreted as a convenient indicator of the metabolic phenotype

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(ratio ≥ 1 suggesting extensive metabolizers and ratio < 1 indicating poor metabolizers), our patient can be classified as having an extensive metabolizer phenotype for CYP2D6.[10] Applying this paradigm results in the problem that genetically confirmed ultrarapid metabolizers are assigned to the group of extensive metabolizers and that a phenotypical approach is unable to distinguish ultrarapid metabolizers from extensive metabolizers.

Therefore, genetic testing was a strongly reasonable next step and revealed a (clinically expected) CYP2D6 ultrarapid metabolizer status with markedly increased enzyme activity.

Several hypothetical explanations for our findings must be addressed. The first of these is that noncompliance of the patient resulted in insufficient plasma levels. This explanation was excluded by administering the drugs on the psychiatric ward, monitoring their intake, and ensuring the act of swallowing. There was never a doubt that the patient took the medication.

The second is that reduced intestinal absorption due to enhanced transporter protein activity such as P-glycoprotein altered plasma levels of the administered drugs. This explanation was excluded by measuring plasma levels of venlafaxine and *O*-desmethylvenlafaxine 60, 120, and 240 minutes after intake and showing high levels of both venlafaxine and *O*-desmethylvenlafaxine, although venlafaxine, but not *O*-desmethylvenlafaxine, is known to be an inducer of drug efflux transporter expression, which increases the potential of drug-drug interactions.[11]

The third consideration to address was the inability to maintain stable plasma concentrations for any of the administered drugs. Phenotypically, our patient can be assumed to be a multiple ultrarapid metabolizer, namely for CYP1A2, CYP2D6, and CYP3A4.

However, in describing the enzyme activity phenotypically, it must be taken into consideration that drug metabolism by means of 2 or more cytochrome subsystems (duloxetine and fluvoxamine via CYP1A2 and CYP2D6; aripiprazole and quetiapine via CYP2D6 and CYP3A4) may result in a shift of the usual metabolic pathway to the most active enzyme subsystem.

Likewise, the inability of paroxetine to substantially block CYP2D6 may also have been caused by the ultrarapid metabolizer status because no plasma paroxetine levels sufficient to block CYP2D6 activity were achieved. The high activity of CYP2D6 may be able to "absorb" the particular drugs from their main metabolic pathways (eg, duloxetine is mainly metabolized via CYP1A2 and to a lesser extent via CYP2D6) toward the usually negligible but in case of ultrarapid metabolizer status highly active metabolizing enzyme system. The genetic analysis of this case could only provide the information that at least more than 1 copy of *2 variant was found. Keeping in mind the findings of Dalén et al[2] that up to 13 copies of *CYP2D6* can exist, with a corresponding high activity of CYP2D6, it seems likely that the highly active CYP2D6 pathway "absorbs" the drugs from their major metabolic pathways.

In summary, the phenomenon of a highly active CYP2D6 isoenzyme is a challenge for every psychiatrist. In our patient, neither daily doses above the approval limit nor the well-directed use of pharmacokinetic blockade of the cytochrome system was able to improve clinical response. Only with a therapeutic regimen that bypasses liver function was partial remission finally achieved. Considering the normal activity of CYP2C19 in our patient, and that very high activity of CYP2D6 can result in increased metabolism of the substances via usually negligible metabolic byways, it is possible that drugs exclusively metabolized by CYP2C19 or other CYP isoenzymes (like agomelatine) or drugs that have no CYP-related metabolism such as milnacipran may exert sufficient antidepressant effects in patients with this genetic condition.

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