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SPECIAL ISSUE

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The impact of the CYP2D6-polymorphism on dose recommendations for current antidepressants

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Abstract Cytochrome P450 CYP2D6 represents an extensively characterized polymorphic drug-metabolizing enzyme. The CYP2D6-gene is highly polymorphic and more than 70 different alleles are known currently. The activity of the enzyme markedly varies among individuals from poor to intermediate and extensive up to ultrarapid metabolism on the basis of the polymorphism of the CYP2D6 gene. Association studies provide growing evidence for the clinical importance of the CYP2D6 polymorphism investigating whether the CYP2D6 genotype distribution differs from that of the normal population either in patients with marked adverse effects or in nonresponders during treatment with CYP2D6 substrates. However, these scientifically important studies present less information for dose adjustments necessary to individualize pharmacotherapy in a given clinical case. With respect to psychopharmacological drug metabolism several antidepressants were characterized as being CYP2D6 substrates. Thus, this review summarizes dose recommendations of current antidepressants.

Key words CYP2D6 · cytochrome P450 · polymorphism · antidepressant therapy

Introduction

The CYP2D6-metabolizing capacity of an individual is mainly determined by the number of fully functional alleles per genome [62]. Thus, if at least one fully functional allele (*EM) is present, an extensive metabolism (EM) phenotype usually results (genotype *EM/*X). If a person inherits two null alleles (*0/*0)—null alleles do not encode a functional gene product —CYP2D6 activity will be absent, leading to a poor metabolizer phenotype (PM; 7% of the White German population). If an *IM (intermediate)allele is not balanced by an *EM allele (*IM/*PM or *IM/*IM genotype), the metabolic capacity is frequently within the intermediate range [61,82]. Ultrarapid metabolizer (UM) capacity can be caused by amplification of functional alleles with high expression of active enzyme, the latter being found in about 3.5% of White subjects. Whereas prediction of a PM phenotype from the CYP2D6 genotype is very accurate and reliable, considerable overlap exists in the metabolizing capacity of other genotypes for reasons not yet understood. Thus, most dose recommendations summarized below refer to the PM vs. EM phenotype and less frequently to the UM phenotype.

Metabolization of antidepressants, contribution of CYP2D6 and resulting dose recommendations (see also Table I for dose recommendations depending on CAYP2D6 genotype)

Amitryptiline

Amitryptiline is demethylated to the principle active metabolite Nortriptyline [8]. This demethylation is mediated by CYP2C19 [5], by smoking induced enzymes such as CYP1A2 [48] and by other CYP enzymes, including CYP2D6 [13, 48]. Hydroxylation of AT is catalysed primarily by CYP2D6 [47, 48, 56]. CYP2C9 and CYP3A4 contribute to the metabolism of amitryptiline as shown in vitro. Based on two studies [3, 5] PMs of CYP2D6 ought to receive about 50% of the manufacturers' recommended dose [41].

Bupropion

The monocyclic antidepressant bupropion, which is frequently used for smoking deprivation, is metabo-

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Table 1 Dose recommendations for antidepressants depending on CYP2D6-genotype

Substance	Dose recommendation for genotype
Amitriptiline	PMs: 50% of manufacturers' recommended dose
Bupropion	No dose recommendation
R/S-, S-Citalopram	No dose recommendation
Clomipramine	PMs: 60% of manufacturers' recommended dose EMs: 120% of manufacturers' recommended dose
Desipramine	PMs: 30% of manufacturers' recommended dose UMs: higher than average dose, therapeutic drug monitoring is recommended
Doxepin	Unknown
Fluoxetine	PMs: 70 % of the average dose at the beginning EMs: 110% of the average dose at the beginning Under steady state conditions differences between PMs and EMs are reduced.
Fluvoxamine	PMs: 60% of the average dose at the beginning EMs: 120% of the average dose at the beginning Under steady-state conditions differences between PMs and EMs are reduced
Imipramine	PMs: evidence based data exists only for the dose range 25-100 mg and for PMs 30% of the average dose was recommended
Maprotiline	PMs: 40% of the average dose EMs: 130% of the average dose
Mianserin	PMs: 70% of the average dose IMs: 90% of the average dose EMs: 110% of the average dose UMs: up to 300% of the average dose. For UMs, dose adjustment under therapeutic drug monitoring was recommended. Under steady-state conditions differences between CYP2D6 genotypes are reduced
Mirtazapine	So far no dose corrections are recommended
Moclobemide	no dose recommendation
Nortriptyline	PMs: 50% of the average recommended dose IMs: 100% of the average recommended dose EMs: 120% of the average recommended dose UMs: up to 230% of the average recommended dose Therapeutic drug monitoring was recommended especially for Ums
Paroxetine	PMs: 20% and 70% of the average dose EMs: 130% and at steady-state conditions 110% of the average dose. Under steady-state differences between CYP2D6 genotypes are reduced
Reboxetine	No dose recommendation
Setraline	No dose recommendation
Trazodone	No dose recommendation
Trimipramine	No dose recommendation
Venlafaxine	PMs: 20% of the average dose EMs: up to 130% of the average dose

lized to the active hydroxy-bupropion, threohydro-Bupropion and the inactive erythrohydro-bupropion. Clinical data suggested that CYP2D6 is not involved in biotransformation of bupropion [40, 60]. Thus no dose recommendations can be given for specific CYP2D6 genotypes.

R/S-citalopram, S-citalopram

Primary elimination of citalopram appeared to be mediated by CYP2C19, CYP2D6 and CYP3A4 but secondary demethylation seemed to depend on CYP2D6 exclusively [57, 67]. Citalopram S/R-ratios are higher in CYPC19 PMs indicating that the S-citalopram–the main active isomer of the racemic drug [35]–is preferentially metabolized by CYP2C19. No dose recommendations are recommended in accordance with the CYP2D6 genotype [41].

Clomipramine

Clomipramine, an important inhibitor of CYP2D6, is metabolized to N-desmethyl-clomipramine and, to a lesser extent, to 8-hydroxy-clomipramine. N-desmethyl-clomipramine possesses antidepressive effects by inhibition of the noradrenergic and the serotoneercic reuptake system [76]. Invivo and invitro studies demonstrated that 8-hydroxylation of Clomipramine and desmethyl-clomipramine is catalysed by CYP2D6 [54, 55]. Clomipramine-demethylation appears to be mediated by other CYP enzymes, including CYP2C19, CYP3A4 [55], and CYP1A2 [9, 10, 34]. Clomipramine shows a nonlinear dose–concentration kinetic [43]. A more pronounced dose-dependent increase in serum concentration was found for EMs compared to PMs. This observation suggests that elimination via CYP2D6 is saturable [21]. Dose recommendations are valid only for the medium dose range given in the studies: PMs of substrates of CYP2D6 may require 60% and EMs 120% of the recommended dose.

Desipramine

Desipramine is metabolized to 2-hydroxy-desipramine by CYP2D6 [17, 46, 71]. Desipramine kinetics is nonlinear, resulting in a disproportionate increase in plasma concentration with higher doses. Patients receiving doses above 150 mg should be carefully monitored. Dose recommendations: PMs should receive 30% of the recommended dose and UM may require much higher than average doses. Since relevant data for UMs are insufficient, therapeutic drug monitoring is particularly important for this subgroup [41].

Doxepin

Doxepine is applied as a mixture containing 15% of the more active Z-isomer and 85% of the less active E-isomer. The metabolite *N*-desmethyl-doxepin contributes to the antidepressant effect of the parent drug. According to in vitro data, hydroxylation of E-doxepin is predominantly catalysed by CYP2D6 and CYP1A2 and CYP3A4 are in volved in demethylation [33]. In vivo data, on the impact of CYP2D6 polymorphism are still lacking [41].

Fluoxetine

Fluoxetine is administered as a racemic mixture of equally potent R- and S-Fluoxetine. The parent drug is metabolized to R/S-norfluoxetine. Norfluoxetine is a

potent inhibitor of serotonin reuptake with a four fold longer plasma elimination half-life than that of fluoxetine [30, 79]. Serum concentrations similar to the parent drug are achieved following repeated dosing [2]. Thus, for dose recommendations, the sum of fluoxetine and norfluoxetine concentrations appears to be relevant. CYP2D6 is involved in N-demethylation of potent R- and S-fluoxetine and of the active metabolite S-Nor-Fluoxetine [28, 32]. Fluoxetine is also a potent inhibitor of CYP2D6 [14]. In contrast to single dosing it can be assumed that, under steady-state conditions, CYP2D6 metabolism in EMs is saturated and that the differences between EMs and PMs are reduced. However, no studies on the steady-state kinetics of fluoxetine in EMs and PMs of CYP2D6 have been identified. Dose recommendations for racemic fluoxetine: the initial dose for PMs of CYP2D6 may be 70% and for EMs 110% of the average dose [41].

Fluvoxamine

Fluvoxamine, an important inhibitor of CYP1A2 and CYP2C19, is primarily eliminated via oxidative O-demethylation. O-demethylation of fluvoxamine is evidently catalysed by CYP2D6 and can be inhibited by fluvoxamine itself [69]. Two single-dose studies in EMs and PMs of CYP2D6 revealed incongruent results [15, 69]. Fluvoxamine shows a non-linear pharmacokinetics and differences between PMs and EMs were smaller under steady-state conditions. A decrease in oral clearance with increasing dose in EMs and PMs indicate that other enzyme systems than CYP2D6 are involved in the metabolism [70]. Dose recommendations: at the beginning of treatment, PMs of CYP2D6 should receive 60% and EMs 120% of the average dose. For maintenance dosage, PMs can probably be dosed as EMs [41].

Imipramine

Imipramin is metabolized primarily via N-demethylation to the principle metabolite desipramine and, via 2-hydroxylation, to 2-hydroxy-imipramin. Desipramin is further metabolized to 2-hydroxy-Desipramine [41]. The 2-hydroxylation of imipramine and desipramine is mediated by CYP2D6 [41]. A lack of improvement of depressive symptoms but no increase in frequency and intensity of side effects were reported for PMs compared to EMs [49]. Imipramine and its metabolite desipramine show nonlinear pharmacokinetics. Evidence based data for dose adjustments exists only for the dose range 25–100 mg and for PMs 30% of the average dose was recommended [41].

Maprotiline

The tetracyclic antidepressant maprotiline is metabolized primarily by demethylation to desmethyl-maprotiline, and by hydroxylation to 1- and 3-hydroxy-maprotiline and to 3-hydroxy-desmethyl-maprotiline [12]. CYP2D6 and obviously other CYP enzymes seem to be involved in the elimination [27, 77]. Increased frequency of side effects like seizures and cardiotoxicity were reported for high maprotiline serum concentrations [22, 64]. Thus, similar doses of maprotiline may result in more adverse drug effects in PMs than in EMs [27]. Dose recommendations: according to the data of Firkusny and Gleiter [27], PMs should receive 40% and EMs 130% of the average dose.

Mianserin

The tetracyclic antidepressant mianserin is administered as a racemic mixture and the pharmacological activity of S- is higher than that of R-mianserin. The major elimination metabolisms are N-demethylation, 8-hydroxylation, N-oxidation and glucuronidation. *N*-desmethyl-mianserin is the principle and therapeutically active metabolite. CYP2D6 contributes to the metabolism of S-mianserin and *N*-desmethyl-mianserin but not to the metabolism of R-mianserin [18]. The CYP2D6 contribution to total clearance was less pronounced under steady-state conditions than following single-dose administration [18, 26, 52]. More adverse drug effects were reported for PMs than for EMs after single-dose administration [18]. Dose recommendations: PMs should receive about 70%, IMs 90%, EMs 110% and UMs up to 300% of the average dose. For UMs, dose adjustment under therapeutic drug monitoring was recommended.

Mirtazapine

Mirtazapine is a racemic drug and both enantiomers are pharmacologically active. Its major metabolites are N-desmethyl-mirtazapine, which is three to four times less active than Mirtazapine and the inactive 8-hydroxy-mirtazapine [73]. The contribution of CYP2D6 to the elimination of mirtazapine via hydroxilation is relatively low [19]. In PMs, CYP1A2 also demonstrates activity in the formation of 8-hydroxy-mirtazapine [41] giving room for compensating CYP2D6 metabolic deficiency. So far no dose corrections are recommended for PMs and UMs but further studies on the impact of genetically polmorphic 2D6 have been requested [41].

Moclobemide

The reversible MAO-A inhibitor moclobemide is metabolized via morpholine carbon and nitrogen oxidation, desamination, and aromatic hydroxylation without significant contribution of CYP2D6 [37]. No dose adjustments for CYP2D6 are necessary.

Nortriptyline

Nortriptyline is metabolized via hydroxylation to 10-hydroxy-nortriptyline [1], which is catalysed primarily by CYP2D6 [16, 56, 81]. For nortriptyline a therapeutic window could be defined i.e. very low and very high plasma levels of nortriptyline are associated with a poor clinical outcome [68]. Thus, for therapy with nortriptyline poorer clinical outcome and more adverse effects are expected to be associated with the PM genotype of CYP2D6 and therapeutic failure is expected to occur more frequently in UMs of CYP2D6 due to plasma concentrations below the therapeutic window [6, 7, 20]. Dose recommendations: PMs should receive 50%, IMs about 100%, EMs 120% and UMs up to 230% of the average recommended nortriptyline dose. Therapeutic drug monitoring was recommended especially for UMs in order to adjust the dosage necessary to achieve therapeutic plasma concentrations.

Paroxetine

Paroxetine possesses no pharmacologically active metabolites. Metabolites resulting after oxidation are subsequently sulphated or glucuronidated [31]. Involvement of CYP2D6 was reported for inhibition of CYP2D6 by Paroxetine itself. The CYP2D6-dependent metabolism is saturable and the differences between PMs and EMs are less prominent under steady-state conditions [66]. No clear correlation between paroxetine plasma concentration and antidepressive effect or frequency and intensity of adverse effects could be observed [75]. Kirchheiner et al. recommended for the first dose that PMs should receive 20% and EMs 130% of the average dose [41]. At steady-state conditions PMs should receive 70% and EMs 110% of the average dose.

Reboxetine

The selective noradrenaline (NA) reuptake inhibitor reboxetine is administered as a racemic mixture and metabolized primarily to *O*-desethyl-reboxetine. According to in vitro data the metabolism of both enantiomers is mainly mediated via CYP3A [78]. No differences in plasma concentrations of reboxetine were found in EMs before and after inhibition of CYP2D6 by quinidine indicating that CYP2D6 is not substantially involved in reboxetine metabolism [63]. No dose recommendations were given for CYP2D6 genotypes.

Sertraline

Sertraline is extensively metabolized by liver enzymes to desmethyl-Sertraline, *N*-hydroxy-sertraline and a ketone metabolite. Desmethyl-sertraline posses <5% potency of the parent drug at blocking serotonin (5-HT) reuptake [72]. Other pharmacologically active metabolites are not described [65]. In vitro data indicate that CYP3A4, CYP2B6, CYP2C9, CYP2D6 and CYP2C19 are involved in demethylation of sertraline to desmethyl-sertraline and that the contribution of any individual isoform to the overall metabolism is low [39]. A single dose study in man with CYP2D6 PMs revealed that the disposition of sertraline is not altered in PM of debrisoquin [32, 42]. However, the influence of the CYP2D6 genotype on sertraline metabolism under steady-state conditions remains to be determined. Based on the current data no dose adjustment in relation to the CYP2D6 genotype is recommended [41].

Trazodone

Trazodone is metabolized via oxidative cleavage, hydroxylation and N-oxidation [36, 38]. The main metabolite is *m*-Chlorophenylpiperazine (mCPP) [4, 58]. CYP2D6 participates to a minor extend to the metabolization of trazodone and mCPP [51, 80]. Thus, no dose corrections for CYP2D6 are necessary.

Trimipramine

The tricyclic antidepressant trimipramine, a racemic drug [24, 45], is metabolized to desmethyl-trimipramine, 2-hydroxy-trimipramine, and 2-hydroxy-desmethyl-trimipramine [74]. Both, desmethyl- and hydroxy-trimipramine, are pharmacologically active. The contribution of CYP2D6 to the metabolization of trimipramine remains unclear. The administration of the CYP2D6-inhibitor quinidine prevented the formation of 2-hydroxy-trimipramine during treatment with trimipramine [25] and in accordance with this finding in vitro data implicated a role of CYP2D6 for the hydroxylation of trimipramine [11]. In contrast to these results a study in healthy subjects indicated a significant contribution of CYP2C19 but not of CYP2D6 to the metabolization of trimipramine [23]. Based on the limited data no dose recommendations were given for the treatment with trimipramine.

Venlafaxine

The racemic drug venlafaxine is a potent NA and 5-HT reuptake inhibitor, and both enantiomers are pharmacologically active. It is metabolized to *O*- and *N*-desmethyl-venlafaxine and to *O*- and *N*-didesmethyl-venlafaxine [53]. CYP2D6 significantly contributes to the formation of *O*-desmethyl-venlafaxine [29, 44, 59] with – according to in vitro data [59]—an enantioselectivity for the S-enantiomer of venlafaxine.

Severe adverse arrhythmia has been reported for PMs of CYP2D6 and high plasma concentrations of venlafaxine [44]. Dose recommendations were given based on venlafaxine serum concentrations: Preliminary dose adjustments according to CYP2D6 recommend 20% of the average dose for PMs and up to 130% for EMs [41].

Discussion

A recent review by an expert group advocated routine phenotyping for CYP2D6 expression specifically in psychiatric patients because of the large number of psychotropic agents that are metabolized primarily by this enzyme [50]. However, different factors and lacking data still make CYP2D6-based dose recommendations problematic. Dose recommendations are valid for different doses only if the drug has a linear dose concentration relationship. For substances showing saturation kinetics, e.g. trimipramine, dose recommendations are only valid in the given dose range. Different roles of cytochrome enzymes are also possible for multiple-dosing compared to single-dosing since enzyme saturation or concentration-dependent differences in metabolic pathways can exist. The roll of active metabolites and stereoselective action and/or metabolization of different drugs make predictions on side effects and therapeutic response based on the CYP2D6-genotype more complex. Psychiatric centres for pharmacovigilance with routine phenotyping for CYP2D6 and drug monitoring should be requested in order to collect data in given clinical cases for PM, EM, IM and UM phenotypes. Subsequently routine phenotyping in psychiatry could be reevaluated.

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