
ORIGINAL REPORT

The impact of Cytochrome P450-2D6 genotype on the use and interpretation of therapeutic drug monitoring in long-stay patients treated with antidepressant and antipsychotic drugs in daily psychiatric practice[†]

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SUMMARY

Purpose This retrospective follow-up study investigates whether cytochrome P450-2D6 (CYP2D6) genotype explains variability in plasma concentrations of psychotropic drugs in daily psychiatric practice.

Methods The study population consisted of 62 hospitalised psychiatric patients genotyped for CYP2D6. Primary endpoint was the normalised plasma concentration ratio which was defined as the [measured concentration]/[mean therapeutic concentration] allowing comparison of plasma concentrations of different substrates. Secondary endpoint was a plasma concentration above the therapeutic range. The determinant was CYP2D6 genotype classified as ultrarapid metaboliser (UM), extensive metaboliser (EM), intermediate metaboliser (IM), or poor metaboliser (PM). The relation between CYP2D6 genotype and the normalised plasma concentration ratio was assessed with a linear mixed-effects model after adjustment for the Prescribed Daily Dose (PDD). The risk of having a plasma concentration above the therapeutic range was assessed with a logistic mixed-effects model.

Results For antidepressants, CYP2D6 genotype PM (1.68 (95%CI: 1.01–2.28)) and IM (1.09 (95%CI: 0.77–1.29)) were associated with higher normalised plasma concentration ratios of antidepressants compared to EMs (0.56 (95%CI: 0.26–0.74)). In addition, the risk of a plasma concentration above the therapeutic range was increased for PMs (OR 33.1 (95%CI: 2.0–544.6)) and IMs (OR 8.2 (95%CI: 1.1–60.3)) relative to EMs using antidepressants. CYP2D6 genotype could not clearly explain variability in plasma concentrations of antipsychotics possibly due to a low frequency of therapeutic drug monitoring (TDM) in antipsychotics primarily metabolised by CYP2D6 in daily psychiatric practice.

Conclusions CYP2D6 genotype contributes to clinically relevant variability in plasma concentrations of antidepressants but probably not antipsychotics in daily clinical practice. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — Cytochrome P450-2D6; CYP2D6; genotype; therapeutic drug monitoring; pharmacogenetics

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INTRODUCTION

Therapeutic drug monitoring (TDM) is a tool to optimise the probability of therapeutic response and to minimise the risk of adverse effects in psychiatric patients using antidepressant and antipsychotic drugs.^{1–7} The rationale for TDM is a plasma concentration dependent likelihood of response relationship and a high inter- and intra-individual variability in pharmacokinetics. Plasma concentrations are influenced by many factors including dosage, concomitantly used medication, adherence, smoking and genetics. One of the important genetic factors in psychiatric patients is polymorphism of cytochrome P450-2D6 (CYP2D6). Approximately 5–10% of Caucasian patients can be classified as poor metabolisers (PM) based on lacking CYP2D6 activity caused by two deficient alleles in the *CYP2D6* gene. Gene duplications resulting in high enzyme activity (ultrarapid metabolisers (UM)) are present in 1–10% of Caucasian patients. Subjects with two active alleles are classified as extensive metaboliser (EM) and carriers of one active and one deficient allele are sometimes classified as intermediate metabolisers (IM). This group of IMs is expected to have subpopulation-specific clearance between EMs and PMs.^{4,8–11} Since most antipsychotic and antidepressant drugs are at least partly metabolised by CYP2D6, this may implicate a higher risk of plasma concentrations outside the presumed therapeutic range in a significant proportion of patients treated in psychiatric practice when CYP2D6 genotype is not taken into account.

The relation between CYP2D6 genotype and pharmacokinetics is well established for several antidepressant and antipsychotic drugs. In most of these studies, however, the relationship between CYP2D6 and pharmacokinetics has been investigated for a specific antidepressant or antipsychotic in a small group of highly selected healthy volunteers or patients. The impact of CYP2D6 genotype on the use and interpretation of TDM of antidepressant and antipsychotic drugs in daily psychiatric practice with more complex patients and more complex treatment patterns is relatively unknown.^{2,4,12–19}

This study investigates retrospectively whether CYP2D6 genotype can explain variability in plasma concentrations of antidepressant and antipsychotic drugs in daily psychiatric practice.

METHODS

Setting

The study was conducted in two psychiatric hospitals of approximately 700 beds in total, offering in- and

out-patient psychiatric services covering a population of approximately 200 000 persons. Approximately 450 beds are used for long-stay patients with chronic psychiatric disorders. The hospitals are located in the cities of Assen and Beilen in the Northern part of The Netherlands. The department of clinical pharmacy of the Wilhelmina Hospital Assen, The Netherlands, provides drugs to all in-patients of the two psychiatric hospitals. For each patient a prescription drug history is available listing patient details (age, date of birth, identification and ward), drug details (name of drug and dosage regimen, start and stop date) and prescriber details. In the majority of departments where patients were included the intake of drugs was observed directly.

Plasma concentrations of antidepressants and antipsychotics are measured by the department of clinical chemistry of the psychiatric hospital. For each patient TDM details (date of sampling and the measured plasma concentration of parent compound and relevant metabolites) are available.

The study protocol was in accordance with the declaration of Helsinki and was reviewed and approved by an independent medical ethical committee (TPWO, Arnhem, The Netherlands).

Design and patients

A retrospective follow-up design was used to assess the relationship between CYP2D6 genotype and plasma concentrations of antidepressant and antipsychotic drugs. The potential study population consisted of 138 long-stay patients of whom CYP2D6 genotype was determined in a previous study.²⁰ Inclusion criteria of the previous study were informed consent and availability of at least 180 days of prescription data.

Patients were eligible for the present study if at least one plasma concentration was determined of an antidepressant or antipsychotic drug. This resulted in inclusion of 62 patients. From these patients prescription and TDM data were collected from January 1998 until June 2003.

Outcome measures

Primary endpoint was the normalised plasma concentration ratio. The measured plasma concentration was transformed to a normalised plasma concentration ratio allowing comparison of plasma concentrations of different drugs. The normalised plasma concentration ratio was defined as the measured plasma concentration divided by the mean therapeutic plasma concentration. For example, nortriptyline has

a therapeutic plasma concentration (therapeutic range) of 75–150 µg/L and therefore a mean therapeutic plasma concentration of 112.5 µg/L. For a patient with a plasma concentration of 225 µg/L the normalised plasma concentration ratio therefore, would be 2 (225 µg/L/112.5 µg/L).

Secondary endpoint was a plasma concentration above the presumed upper limit of the therapeutic range. Reference values for the presumed therapeutic range were those as used during daily clinical practice in the psychiatric hospitals where the study was conducted (see Tables 2 and 3). Although there is debate about the therapeutic range for several psychotropic drugs, especially antipsychotics, we choose to use the range as used during daily clinical practice since this is the range the treating psychiatrists use for treatment decisions.

Determinants

Primary determinant was the CYP2D6 genotype. The CYP2D6 genotype was determined by polymerase chain reaction (PCR)-RFLP. Genomic DNA was isolated from EDTA-anticoagulated blood using standard methods. The non-coding alleles CYP2D6*3(A), *4(B), *6(T), *7(E) and *8(G) were investigated using a long-distance and multiplex-PCR as described by Stuvén *et al.*²¹ These variants allow identification of approximately 98.7% of the PMs in a Caucasian population.²² The presence of gene duplication that may lead to ultrarapid metabolism was analysed by an allele-specific PCR and was performed as described by Lovlie *et al.*²³ Only samples with at least one wild-type allele were analysed for CYP2D6 gene duplication. In all experiments positive control samples (DNA samples with known CYP2D6 genotype (*5/*6 and wt/*7) and negative control samples (water) were included. DNA-isolation and genotype procedures were performed under the responsibility of Pharma BioResearch Zuidlaren, The Netherlands. Patients were defined as PM if they were homozygous for non-coding alleles. Patients were defined as UM if gene duplication was detected and mutant alleles were absent. Patients were identified as IM if they were heterozygous with one coding allele and one non-coding allele. All other patients (homozygous for coding alleles) were classified as EM. Another technician checked all obtained results and the interpretation of the results. The CYP2D6 genotyping results were blinded to the researcher and the treating psychiatrist until data analysis.

Data analysis

Pharmacy records and TDM records of antidepressant and antipsychotic drugs were transferred to a database (MS Access) for analysis. Antidepressant and antipsychotic drugs are sometimes metabolised to active metabolites. In that case, plasma concentrations of the active metabolites were added to the parent compound. When plasma concentrations of active metabolites had not been measured those TDM measurements were excluded from the analysis. The main protocol for collecting EDTA-anticoagulated blood samples for TDM refers to blood sampling as trough levels. However, the exact time of collecting the blood sample was not available. Overall, only five measurements of TDM were not taken at steady state concentrations. Exclusion of these measurements did not change the obtained results. Plasma concentrations of antidepressants and antipsychotics were analysed using validated high-performance liquid chromatography analyses. Standard procedures including internal and external quality controls were used for all TDM measurements.

The Anatomical Therapeutic Chemical (ATC) classification was used to identify antipsychotic (ATC: N05A) and antidepressant (ATC: N06A) drugs. Lithium was excluded from the analysis. The Prescribed Daily Dose (PDD) was defined as the administered dosage divided by the Defined Daily Dose (DDD) (PDD = dosage/DDD) according to the WHO guidelines.²⁴ The CYP2D6 metabolic pathway was classified for each antidepressant and antipsychotic drug according to the available evidence. Drugs for which an *in vivo* relationship between CYP2D6 genotype and pharmacokinetic properties has been documented were classified as primarily metabolised by CYP2D6 (primary). Other classifications were drugs *in vitro* at least partly metabolised by CYP2D6 (partly), drugs not metabolised by CYP2D6 (no metabolism by CYP2D6) and drugs without available data on metabolism by CYP2D6 (unknown).⁴ All determined plasma concentrations of antidepressants and antidepressants were taken into account.

The association between CYP2D6 genotype and the normalised plasma concentration ratio was assessed with a linear mixed-effects model after adjustment for differences in PDD. Results were expressed as a mean normalised plasma concentration ratio together with a 95% confidence interval (95%CI). The simultaneous two-sided 95% bootstrap percentile confidence intervals for the mean normalised plasma concentration ratios were computed using 200 replications. Bootstrap samples were obtained by random sampling patients

(with replacement) from the population. The relative risk of a plasma concentration above the therapeutic range was estimated with a logistic mixed-effects model and expressed as an odds ratio (OR) with a 95%CI using EM as the reference group. The mixed-effects models were used because in some patients there were more than one plasma concentration available and therefore the data were not independent. Mixed-effects models make adjustments for multiple measurements in the same subject. A *p*-value of 0.05 or less was regarded as significant. Data were analysed separately for antidepressants and antipsychotics. Data were analysed using S-plus 6.2 ('correlatedData' library).^{25,26}

RESULTS

In our study population (*n* = 62) we found extensive, intermediate, poor and ultrarapid metabolism for CYP2D6 in 51.6, 33.9, 11.3% respectively 3.2% of the included patients. These frequencies are as expected in a Caucasian population.¹⁰ The characteristics of the included patients are summarised in Table 1.

In the 62 included patients, 530 plasma concentrations of antidepressant (*n* = 90) and antipsychotic drugs (*n* = 440) had been measured. The plasma concentration of the active metabolite of risperidone was not available in one patient and that measurement was therefore excluded from the analysis. Clomipramine, fluvoxamine and nortriptyline were the most

frequently determined antidepressants. Clozapine, zuclopenthixol and olanzapine were the most frequently determined antipsychotics. All TDM measurements of antidepressants but only 8.6% of TDM measurements of antipsychotics were from drugs for which an *in vivo* relationship between CYP2D6 genotype and pharmacokinetic parameters has been documented. TDM was not performed more often in PMs, IMs or UMs compared to EMs. An overview of the number of determined plasma concentrations in antidepressants and antipsychotics per genotype is shown in Tables 2 and 3.

Figure 1A shows that for antidepressants CYP2D6 genotype PM (1.68 (95%CI: 1.01–2.28)) as well as genotype IM (1.09 (95%CI: 0.77–1.29)) were associated with significantly higher dosage adjusted normalised plasma concentration ratios compared to EMs (0.56 (95%CI: 0.26–0.74)). Figure 1B shows that for antipsychotics CYP2D6 genotype PM (1.74 (95%CI: 0.64–2.43)) and IM (1.09 (95%CI: 0.68–1.46)) were not clearly associated with higher dosage adjusted normalised plasma concentration ratios compared to EMs (1.02 (95%CI: 0.70–1.37)). CYP2D6 genotype UM was not associated with decreased plasma concentration ratios of antidepressants (0.43 (95%CI: –0.26–1.28)) or antipsychotics (0.78 (95%CI: 0.71–0.84)).

Table 4 shows that for antidepressants, CYP2D6 genotype PM (OR 33.1 (95%CI: 2.0–544.6)) and IM (OR 8.2 (95%CI: 1.1–60.3)) were associated with an increased risk of plasma concentrations above the therapeutic range compared to EMs. For antipsychotics CYP2D6 genotype PM (OR 12.2 (95%CI: 1.1–134.3)) but not IM (OR 0.8 (95%CI: 0.2–3.3)) was associated with an increased risk of plasma concentrations above the therapeutic range compared to EMs. In total, plasma concentrations above the therapeutic range were found in 8% (3/40), 39% (14/36), respectively 50% (6/12) of measurements of antidepressants in EMs, IMs and PMs and in 13% (35/270), 10% (15/158), respectively 70% (7/10) of measurements of antipsychotics in EMs, IMs and PMs. Plasma concentrations above the therapeutic range were not found for UMs (three plasma concentrations were within the therapeutic range and one plasma concentration was below the therapeutic range).

DISCUSSION

In this retrospective follow-up study, we found that in daily clinical psychiatric practice for antidepressants, PMs and IMs for CYP2D6 have higher plasma concentrations and an increased risk of plasma concentrations

Table 1. Baseline characteristics of the study population (*n* = 62)

Characteristic ^a	<i>n</i>
Age, mean (SD)	53 (15)
Gender (%)	
Male	25 (40.3)
Female	37 (59.7)
Ethnicity (%)	
Caucasian	59 (95.2)
Asian	1 (1.6)
Middle Eastern	1 (1.6)
African	1 (1.6)
Observation period, mean in years (SD)	3.66 (1.29)
Genotype (%)	
Extensive metaboliser	32 (51.6)
Intermediate metaboliser	21 (33.9)
Poor metaboliser	7 (11.3)
Ultrarapid metaboliser	2 (3.2)

^aInformation on age and follow-up was determined from the prescription files; information on ethnicity was determined by interviewing the assistant nurse of the patient; information on genotype was determined by PCR-RFLP.

Table 2. Determined plasma concentrations of antidepressants per genotype

Drug ^a	Range µg/L (mean) ^b	CYP2D6 ^c	Number of determined plasma concentrations (number of patients)			
			UM ^d (n)	EM (n)	IM (n)	PM (n)
Amitriptyline + Nortriptyline	100–250 (175)	Primary	—	1 (1)	1 (1)	—
Clomipramine + Desmethylclomipramine	150–300 (225)	Primary	1 (1)	15 (5)	31 (8)	1 (1)
Doxepin + Nordoxepin	200–350 (275)	Primary	—	6 (1)	—	—
Fluvoxamine	50–250 (150)	Primary	1 (1)	15 (4)	4 (3)	—
Nortriptyline	75–150 (112.5)	Primary	—	1 (1)	—	11 (2)
Paroxetine	10–75 (42.5)	Primary	—	1 (1)	—	—
Venlafaxine + Desmethylvenlafaxine	250–750 (500)	Primary	—	1 (1)	—	—
Total antidepressants	—	—	2	40	36	12
Total patients	—	—	2	14	12	3

^aParent compound and determined active metabolites. Other active metabolites were not determined.

^bRange: therapeutic range as used during daily clinical practice.

^cCYP2D6 primary, drugs for which an *in vivo* relationship between CYP2D6 genotype and pharmacokinetic parameters has been documented.

^dUM, ultrarapid metaboliser; EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.

Table 3. Determined plasma concentrations of antipsychotic drugs per genotype

Drug ^a	Range µg/L (mean) ^b	CYP2D6 ^c	Number of determined plasma concentrations (number of patients)			
			UM ^d (n)	EM (n)	IM (n)	PM (n)
Clozapine	200–600 (400)	Partly	—	244 (11)	141 (9)	2 (1)
Fluphenazine	1–20 (10.5)	Unknown	—	—	1 (1)	—
Haloperidol	5–40 (22.5)	Primary	2 (1)	3 (3)	4 (2)	—
Olanzapine	10–50 (30)	Partly	—	3 (2)	1 (1)	7 (2)
Risperidone + 9-OH-risperidone	10–95 (52.5)	Primary	—	3 (2)	1 (1)	1 (1)
Perphenazine	1–20 (10.5)	Primary	—	2 (1)	—	—
Periciazine	5–30 (17.5)	Unknown	—	1 (1)	—	—
Quetiapine	50–500 (275)	Partly	—	2 (1)	—	—
Zuclopentixol	2–15 (8.5)	Primary	—	12 (4)	10 (2)	—
Total antipsychotics	—	—	2	270	158	10
Total patients	—	—	1	25	16	4

^aParent compound and determined active metabolites. Other active metabolites were not determined.

^bRange: therapeutic range as used during daily clinical practice.

^cCYP2D6 primary, drugs for which an *in vivo* relationship between CYP2D6 genotype and pharmacokinetic properties has been documented; partly, at least *in vitro* partly metabolised by CYP2D6; unknown, metabolism unknown.

^dUM, ultrarapid metaboliser; EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser.

above the therapeutic range compared to EMs. In contrast, CYP2D6 genotype could not clearly explain variability in plasma concentrations of antipsychotics.

There are some limitations to these results. Firstly, the number of patients with extreme rates of metabolism and the number of measured plasma concentrations were relatively small. TDM measurements were gathered during a period of 5 years. This means that the treating psychiatrists in our setting did not use TDM frequently. Furthermore, we could only study 2 UMs with 4 measurements of TDM and 7 PMs with 22 measurements of TDM. Despite these low numbers

significant results were obtained for PMs but this needs confirmation in a larger number of patients. The number of UMs and the corresponding records of TDM were too low to allow any conclusion. Therefore, the results of the UMs are not taken into account in this discussion. Secondly, apart from genotype several other variables can contribute to changes in plasma concentration of psychotropic drugs. For example, liver and kidney function and concomitantly used medication were not taken into account. Furthermore, plasma concentrations of antidepressants and antipsychotics were collected retrospectively and therefore

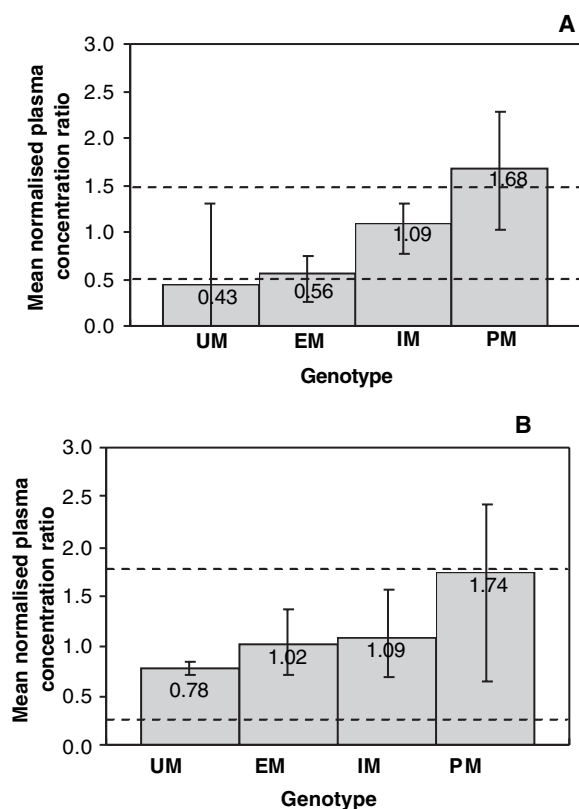


Figure 1. PDD-adjusted mean normalised plasma concentration ratio with 95%CI according to CYP2D6 genotype (UM, ultrarapid metaboliser; EM, extensive metaboliser; IM, intermediate metaboliser; PM, poor metaboliser). Dotted horizontal line presents the mean normalised plasma concentration ratios of the upper and lower limits of the mean therapeutic range. **A:** Antidepressants. **B:** Antipsychotics

Table 4. Relative risk of plasma concentrations above the therapeutic range

OR ^a (95%CI) ^b above therapeutic range	
Antidepressants	<i>n</i> = 23 (25.6% of all measurements)
Extensive metaboliser	1 (reference)
Intermediate metaboliser	8.2 (1.1–60.3)
Poor metaboliser	33.1 (2.0–544.6)
Ultrarapid metaboliser	NE ^c
Antipsychotics	<i>n</i> = 57 (13.0% of all measurements)
Extensive metaboliser	1 (reference)
Intermediate metaboliser	0.8 (0.2–3.3)
Poor metaboliser	12.2 (1.1–134.3)
Ultrarapid metaboliser	NE

^aOR, odds ratio.

^bCI, confidence interval.

^cNE, not estimable.

blood samples were not taken at the same interval after starting a drug or changing a dosage regimen; also TDM was performed in different substrates and linear dose concentration relations are not established in all of these substrates (for example, clomipramine and fluvoxamine).⁸ Finally, increased plasma concentrations do not necessarily reflect an increased risk of adverse events or treatment failure because of pharmacodynamic variability, for example in receptors. However, analysis without these variables probably does not influence the obtained results because differences in these variables most likely influence different genotype groups in a comparable way. Thirdly, we compared plasma concentrations of different psychotropic drugs by using a normalised plasma concentration ratio. To our knowledge this ratio has not been used before and therefore these results have to be interpreted carefully. The therapeutic range of individual psychotropics might manipulate the mean normalised plasma concentration ratio of antidepressants and antipsychotics apart from CYP2D6 genotype. To analyse whether this problem occurs we calculated the mean normalised plasma concentration ratio with and without individual psychotropics. The trend for the mean normalised concentration ratios of PMs and IMs compared to EMs was consistent in these analyses and in general the measurements of TDM in individual patients showed the same consistent trend for PMs and IMs compared to EMs as well. Based on these observations we believe that the normalised concentration ratio can be used in this analysis. Finally, there is debate for several psychotropic drugs, especially atypical antipsychotics, about the therapeutic range. We have chosen to use the range as used during daily clinical practice in the institutions where the study was conducted, since this is the range the treating psychiatrists use for treatment decisions. However, different therapeutic ranges are reported especially for antipsychotics and these ranges can change the obtained result as shown in the next part of this discussion.²⁷

The lack of association between CYP2D6 genotype and plasma concentrations of antipsychotics may be explained by the antipsychotics most frequently determined in daily clinical practice. Only 38 (8.6%) of 440 measurements of TDM of antipsychotics were determined in antipsychotics for which an *in vivo* relationship between CYP2D6 genotype and pharmacokinetic parameters has been documented. Furthermore, 387 (88%) of 440 measurements of TDM were determined in patients using clozapine. The impact of CYP2D6 genotype on plasma concentrations of clozapine is minor.⁴ Apparently, TDM was not used

frequently for antipsychotics primarily metabolised by CYP2D6. Metabolism of antipsychotics partly metabolised by CYP2D6 is possibly compensated by other enzymatic pathways resulting in plasma concentrations comparable to EMs. Analysis of plasma concentrations of antipsychotics primarily metabolised by CYP2D6 was not possible due to low numbers of plasma concentrations in this group of antipsychotics. The increased risk of a plasma concentration above the therapeutic range for antipsychotics is caused by the narrow therapeutic range for olanzapine (10–50 µg/L) as used as the reference value in the psychiatric hospitals. A recent review suggests a therapeutic range for olanzapine from 20 to 80 µg/L.²⁷ The risk of a plasma concentration above the therapeutic range for antipsychotics is not significantly increased when we use this therapeutic range. Taken together, we conclude that in this population CYP2D6 genotype could not clearly explain variability of plasma concentrations of antipsychotic drugs.

In our study the treating psychiatrists were not aware of the CYP2D6 genotype of their patients and therefore the choice of drug and the dosage of these drugs were not individualised according to the CYP2D6 metabolic status. TDM could not prevent the increased risk of elevated plasma concentrations and TDM was not performed more often in UMs, IMs and PMs. We expected that TDM was performed more often in IMs and PMs because of their increased risk of plasma concentrations above the therapeutic range. We assumed that the treating psychiatrists would adjust their treatment on the basis of these increased plasma concentrations in order to prevent concentration-dependent adverse events. It seems reasonable to expect follow up of these adjustments by another request for TDM but apparently this did not occur. Unfortunately, we did not know whether the increased plasma concentrations of antidepressants were associated with more adverse events or treatment failure because this information was not available. Therefore, it is difficult to extrapolate these results to the actual clinical impact for psychiatric patients but these data suggest that the treating psychiatrists had at least problems to trace back abnormal results of TDM to patients with pharmacokinetic disturbances. Genotyping for CYP2D6 before starting pharmacotherapy makes it possible to identify patients with an increased risk of increased plasma concentrations of antidepressants. Patients classified as IM or PM can be supported by more frequent measurements of TDM in drugs primarily metabolised by CYP2D6. Future studies have to determine whether this approach can prevent concentration-dependent adverse events.

KEY POINTS

- CYP2D6 genotype PM and IM is associated with increased plasma concentrations of antidepressant drugs.
- CYP2D6 genotype is a determinant for plasma concentrations above the therapeutic range of antidepressant drugs.
- CYP2D6 genotype cannot explain clearly the variability in plasma concentrations of antipsychotic drugs possibly due to a low frequency of TDM in antipsychotics primarily metabolised by CYP2D6 in daily psychiatric practice.
- CYP2D6 genotyping before starting pharmacotherapy could possibly identify patients with pharmacokinetic disturbances and therefore prevent increased plasma concentrations and concentration-dependent adverse events.

The influence of CYP2D6 genotype IM on plasma concentrations is relatively unknown. This study suggests that IMs for CYP2D6 also have increased plasma concentrations of antidepressants and an increased risk of plasma concentrations above the therapeutic range. Therefore, the obtained result suggests that the possible target population of CYP2D6 genotyping becomes much larger in patients using antidepressants.

In conclusion, CYP2D6 genotype is associated with increased plasma concentrations and an increased risk of plasma concentrations above the therapeutic range in patients using antidepressants. In daily clinical practice, CYP2D6 genotype cannot explain clearly the variability in plasma concentrations of antipsychotic drugs because TDM was not used frequently in antipsychotics primarily metabolised by CYP2D6. In patients using antidepressants, dose adjustments and choice of drug according to CYP2D6 genotype could possibly prevent increased plasma concentrations and concentration-dependent adverse events. Prospective trials are necessary to establish the clinical value of genotyping CYP2D6 before starting pharmacotherapy in specific patients and psychiatric patients in general.

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