Prevalence of Patients Using Drugs Metabolized by Cytochrome P450 2D6 in Different Populations: a Cross-Sectional Study

Hans Mulder, Eibert R Heerdink, Elsje E van Iersel, Frederik W Wilmink, and Antoine CG Egberts

BACKGROUND: Despite a large number of studies investigating the potential clinical relevance of CYP2D6 genotyping in preventing treatment failure (eg, insufficient efficacy and/or unacceptable adverse effects), the prevalence of patients using drugs metabolized by that isoenzyme is relatively unknown.

OBJECTIVE: To investigate the prevalence of patients in different populations using drugs metabolized by CYP2D6.

METHODS: In this cross-sectional study, 6 different patient populations were investigated: general, general hospital, geriatric, psychogeriatric, psychiatric, and mentally retarded. From every population, 150 adults using at least one drug were randomly selected. Primary outcome was the prevalence of patients using at least one drug metabolized by CYP2D6. The prevalence of patients using at least one CYP2D6 substrate in different populations was compared with the general population using χ^2 statistics. Data were expressed as a relative risk with a 95% confidence interval.

RESULTS: Patients from the general hospital (RR 1.81; 95% CI 1.26 to 2.62), geriatric patients (RR 2.16; 95% CI 1.26 to 2.62), psychogeriatric patients (RR 2.31; 95% CI 1.63 to 3.27), and psychiatric patients (RR 2.44; 95% CI 1.73 to 3.44) were treated more frequently with at least one drug metabolized by CYP2D6 compared with patients in the general population. Approximately 50% of psychiatric (52%), psychogeriatric (49%), and geriatric (46%) patients used at least one drug metabolized by CYP2D6. In total, 416 drugs metabolized by CYP2D6 were prescribed, with 257 (62%) of these classified as an antidepressant (Anatomical and Therapeutic Chemical [ATC] category N06A) or antipsychotic (ATC N05A).

CONCLUSIONS: Several patient populations (eg, psychiatric, psychogeriatric, geriatric) have a high prevalence of patients treated with at least one drug metabolized by CYP2D6. This study does not provide evidence regarding the clinical evidence of CYP2D6 genotyping, but shows that, if CYP2D6 genotyping is relevant for patient care, the highest probability of cost-effectiveness will, most likely, be in specific populations.

KEY WORDS: antidepressants, antipsychotics, cytochrome P450 2D6.

Ann Pharmacother 2007;41:408-13.

Published Online, 6 Mar 2007, *www.theannals.com*, DOI 10.1345/aph.1H482

Genotyping of CYP2D6 has been mentioned as one of the first pharmacogenetic tests to be implemented in daily clinical practice to improve the outcomes of pharmacotherapy.[1,2] The suggested high clinical relevance of CYP2D6 genotyping originates, among other reasons, from a relatively high prevalence of variant alleles in the white population, as well as the expected high prevalence of use of drugs metabolized by CYP2D6. Approximately 5–10% of white people can be classified as poor metabolizers (PMs) by lacking CYP2D6 activity and 1–10 % as ultrarapid metabolizers (UMs) by gene duplication resulting in high enzyme activity.[3] Furthermore, several reports have suggested that CYP2D6 is involved in the metabolism of approximately 20–30% of all available drugs.[4,5] Therefore, in white populations, millions of people are potentially at risk for compromised metabolism and the associated clinical complications.

The prevalence of variant alleles among white populations is high enough (10–20%) to suggest that preventive CYP2D6 genotyping may be useful in daily clinical practice. However, for genotyping to be cost-effective, a high prevalence of patients using drugs metabolized by CYP2D6 is essential, together with clinical relevance. Despite large numbers of studies investigating the clinical relevance of CYP2D6 genotyping, the prevalence of drugs metabolized by this isoenzyme in different patient populations is relatively unknown.[6,7]

Many drugs metabolized by CYP2D6 are antidepressants or antipsychotics, making the isoenzyme a potentially important factor in psychiatric practice. However, the impor-

Author information provided at the end of the text.

tance of CYP2D6 might be overestimated because many recently introduced antidepressants (eg, citalopram, sertraline) and antipsychotics (eg, olanzapine, quetiapine) are not primarily metabolized by CYP2D6.[8] If the prevalence of drugs metabolized by CYP2D6 is not as high as expected, this would reduce the likelihood of genotyping being cost-effective in daily clinical practice. The objective of this study was to investigate the prevalence of patients in different patient populations using drugs metabolized by CYP2D6.

Methods

DESIGN AND POPULATION

A cross-sectional design was used to assess the prevalence of patients in different populations using CYP2D6 substrates. The study was conducted within the Department of Clinical Pharmacy of the Wilhelmina Hospital Assen, located in the northern part of the Netherlands. This pharmacy is responsible for the pharmaceutical care of approximately 3000 patients admitted to 15 healthcare institutions. Data from the general population were retrieved from the Kring community pharmacy Zuidlaren, also located in the northern part of the Netherlands.

Six different populations were investigated based on the institution or ward where they were hospitalized:

1. patients from the general population identified by their prescription record as present in the drug dispensing database of a community pharmacy without knowledge of their diagnosis;
2. patients hospitalized in a general hospital and admitted to internal medicine, neurology, pulmonary disease, and cardiology wards;
3. geriatric patients admitted to a nursing home with a somatic diagnosis;
4. psychogeriatric patients admitted to a general psychiatric hospital on wards for older patients with chronic mental disorders according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th revision (DSM-IV)[9];
5. psychiatric patients admitted to a general psychiatric hospital on wards for patients with chronic mental disorders according to DSM-IV; and
6. mentally retarded patients admitted to long-term care facilities for this population.

To be included in the study, patients had to use at least one drug and be older than 18 years. Use of at least one drug was required because, in the general population, a substantial number of people do not use any drug compared with the number not using any drug in other populations. Inclusion of these people would have resulted in a deflated prevalence of patients using at least one drug metabolized by CYP2D6 in the general population compared with the other populations. In all populations, 150 patients were randomly selected. The study was performed in compliance with the requirements of the human research committee of the institutions regarding noninterventional studies with anonymized patient data. Prescription data for all patients were collected in June 2006. The prescription data present information on the current use of prescribed medications at the time of analysis.

OUTCOME MEASURES

The primary endpoint was the point prevalence of use of at least one drug metabolized by CYP2D6. The secondary endpoint was the association between the point prevalence of CYP2D6 substrates and the age of the selected patients. From the information in the prescription file, a case record form was completed for each patient. Information gathered included institution, year of birth, sex, number of drugs, number of CYP2D6 substrates, and the name of the CYP2D6 substrates together with the first 3 characters of the Anatomical Therapeutic Chemical (ATC) classification (eg, N06A for antidepressant drugs).

A drug was classified as a substrate of CYP2D6 when it was listed in the Flockhart CYP drug interaction table, published by the Indiana University Department of Medicine.[10] This table is updated frequently (at least a few times a year), and drugs are included if there is published evidence of metabolism, at least partly, by CYP2D6. To calculate the total proportion of CYP2D6 substrates, we included all oral and parenteral drugs approved by the Dutch Medicines Evaluation Board or the European Medicines Evaluation Authority. Dermatologic preparations, stomatological preparations, oromucosal preparations, and indifferent (without pharmacologic active compound) oropharyngeal, nasal, and ocular preparations were excluded because of their limited systemic absorption. Depot injections and drugs prescribed to be used as needed were considered currently prescribed drugs.

DATA ANALYSIS

The prevalence of patients in different populations using at least one CYP2D6 substrate was compared with the prevalence of use in the general population (reference), using χ^2 statistics. The risk of being treated with at least one drug metabolized by CYP2D6 in a specific patient population compared with that in the general population was expressed as a relative risk together with 95% confidence interval. The association between treatment with at least one drug metabolized by CYP2D6 and age was addressed similarly by comparing age groups, using patients younger than 30 years as the reference group. A p value of 0.05 or less was regarded as significant. Data were analyzed using SPSS 11.0. In the geographical region of this study, we found prevalences of PMs and UMs of 11% and 4%, respectively.[11]

With the prevalence of patients in different populations using at least one CYP2D6 substrate, it is possible to calculate a parameter in analogy to the parameter number needed to treat. We termed this parameter number needed to genotype (NNG) to identify a patient with compromised metabolism by CYP2D6 (PM or UM) who is treated with at least one drug metabolized by CYP2D6.[12]

In total, 15% of the selected patients (11% PM + 4% UM) were expected to have compromised metabolism by CYP2D6. The NNG to find one patient with compromised metabolism by CYP2D6 was 6.7 (1/0.15). Further, not all patients with compromised metabolism by CYP2D6 are treated with a drug metabolized by CYP2D6. Therefore, the NNG to find one patient with compromised metabolism by CYP2D6 who is treated with at least one drug metabolized by CYP2D6 was calculated by dividing 6.7 by the determined prevalence.

Results

In total, we analyzed the drug use profiles of 900 patients divided over 6 different patient populations. Geriatric patients used the largest number of drugs per patient (7.6), and patients from the general population used the smallest number of drugs per patient (3.0). Table 1 shows that patients from the general hospital (RR 1.81; 95% CI 1.26 to 2.62), geriatric patients (RR 2.16; 95% CI 1.26 to 2.62), psychogeriatric patients (RR 2.31; 95% CI 1.63 to 3.27), and psychiatric patients (RR 2.44; 95% CI 1.73 to 3.44) were treated more frequently with at least one drug metabolized by CYP2D6 compared with the general population.

Approximately 50% of psychiatric (52%), psychogeriatric (49%), and geriatric (46%) patients used at least one drug metabolized by CYP2D6. The NNG to identify a patient with compromised metabolism by CYP2D6 who is treated with at least one drug metabolized by that isoenzyme is 13 for these populations, given that approximately 50% of all patients are currently treated with at least one drug metabolized by CYP2D6 (1/(0.15•0.50) = 13). Including the intermediate phenotype (patients with 1 mutant allele; prevalence approximately 33%[13]), the NNG is 4 for psychiatric, psychogeriatric, and geriatric patients (1/(0.15 + 0.33) • 0.50).

Table 2 shows that the age of patients was not associated with the risk of being treated with at least one drug metabolized by CYP2D6.

Figure 1 provides an overview of the different CYP2D6 substrates (total numbers) prescribed in the different patient populations. In total, 416 different drugs metabolized by CYP2D6 were prescribed, of which 257 (62%) were classified as antidepressants (ATC N06A) or antipsychotics (ATC N05A), most frequently in psychiatric, psychogeriatric and geriatric patients. β-Blockers (ATC C07A) were the most frequently used drugs metabolized by CYP2D6 in geriatric patients and patients from the general population. The overall proportion of drugs metabolized by CYP2D6 in the 6 different patient populations—general population (7.0%), general hospital 7.0%), geriatric (7.8%), mentally retarded (7.9%), psychogeriatric (8.6%), and psychiatric (11.8%)—was not as high (20– 30%) as suggested in the literature.[4,5]

Discussion

In this cross-sectional study, we found that the prevalence of patients treated with at least one drug metabolized by CYP2D6 was high in psychiatric patients (52%), psychogeriatric patients (49%), and geriatric patients (46%) compared with the prevalence in the general population (21%). The prevalence of patients using drugs metabolized by CYP2D6 was not associated with age.

Some issues must be addressed to interpret the results properly. First, we used the Flockhart table as a reference for determining whether drugs are a substrate of CYP2D6. We compared the table with 3 other references for CYP2D6 substrates.[14-16] This comparison resulted in 5 discrepancies, with possible implications for the results in relation to the drugs mentioned in Figure 1: metoclopramide, promethazine, mirtazapine, tolterodine, and zuclopenthixol. Zuclopenthixol, tolterodine, and mirtazapine are not present in the Flockhart table, despite the available evi-

Table 1. Patient Characteristics[a]

Population	Mean Age, y (range)	Male, %	Mean Number of Drugs (range)	% Treated with ≥1 CYP2D6 Metabolizer	RR (95% CI) CYP2D6
General	55 (18–87)	34	3.0 (1–10)	21 (32/118)[b]	reference
General hospital	69 (20–95)	50	6.7 (1–20)	39 (58/92)	1.81 (1.26 to 2.62)
Geriatric	77 (32–98)	39	7.6 (1–20)	46 (69/81)	2.16 (1.26 to 2.62)
Psychogeriatric	69 (41–91)	38	7.2 (1–24)	49 (74/76)	2.31 (1.63 to 3.27)
Psychiatric	47 (21–75)	61	5.5 (1–15)	52 (78/72)	2.44 (1.73 to 3.44)
Mentally retarded	48 (20–84)	59	3.4 (1–9)	22 (33/117)	1.03 (0.67 to 1.59)

[a]N = 150
[b]Number of patients with at least one drug metabolized by CYP2D6/number of patients without at least one drug metabolized by CYP2D6.

dence on metabolism by CYP2D6, and promethazine and metoclopramide are part of the table, although there is only in vivo evidence for metabolism by CYP2D6.[17-22] Unfortunately, there is no clear-cut definition of the classification of primary CYP2D6 substrate and evidence for metabolism by CYP2D6 is evolving rapidly for many drugs.

The Flockhart table is updated frequently and presents free, transparent information about the included drugs by linking to PubMed. Therefore, we believe the Flockhart table presents an appropriate source of information for our objective. Second, it should be considered that we analyzed prescription data from patients in the same geographic region. The choice of drugs may be regionally determined; therefore, these data must be extrapolated to other regions carefully. However, the drugs were prescribed in different institutions by a substantial number of prescribers (>40) not participating in the same pharmacotherapy audit meetings. Therefore, we believe the results presented here will not be substantially different in other regions in at least the Netherlands, but probably also in other countries with comparable healthcare settings. Finally, we investigated several patient populations based on institution or ward. These criteria resulted in the inclusion of patients younger than 65 years in the geriatric (n = 23, with 8 pts. aged 60–65 y) and psychogeriatric (n = 47, with 27 pts. aged 60–65 y) population.

We chose these criteria because we wanted to analyze complete patient settings (general population, ward, institution) to identify target populations in which the introduction of CYP2D6 genotyping is most likely to be cost-effective. Analysis of psychogeriatric and geriatric patients without patients younger than 65 years showed results similar to those presented here.

Knowledge about the proportion of drugs metabolized by CYP2D6 is important for implementation of CYP2D6

Table 2. Relative Risk of Treatment with Drugs Metabolized by CYP2D6 in Different Age Groups

Age, y (n)	% of Pts. Treated with ≥1 CYP2D6 Substrate	RR (95% CI) Treatment with Substrate CYP2D6
<30 (52)	37 (19/33)[a]	1 (reference)
30-40 (84)	36 (30/54)	0.98 (0.62 to 1.55)
40-50 (103)	31 (32/71)	0.85 (0.54 to 1.35)
50-60 (208)	38 (78/130)	1.03 (0.69 to 1.53)
>60 (453)	41 (185/268)	1.12 (0.77 to 1.63)

[a]Number of patients with at least one drug metabolized by CYP2D6/number of patients without at least one drug metabolized by CYP2D6.

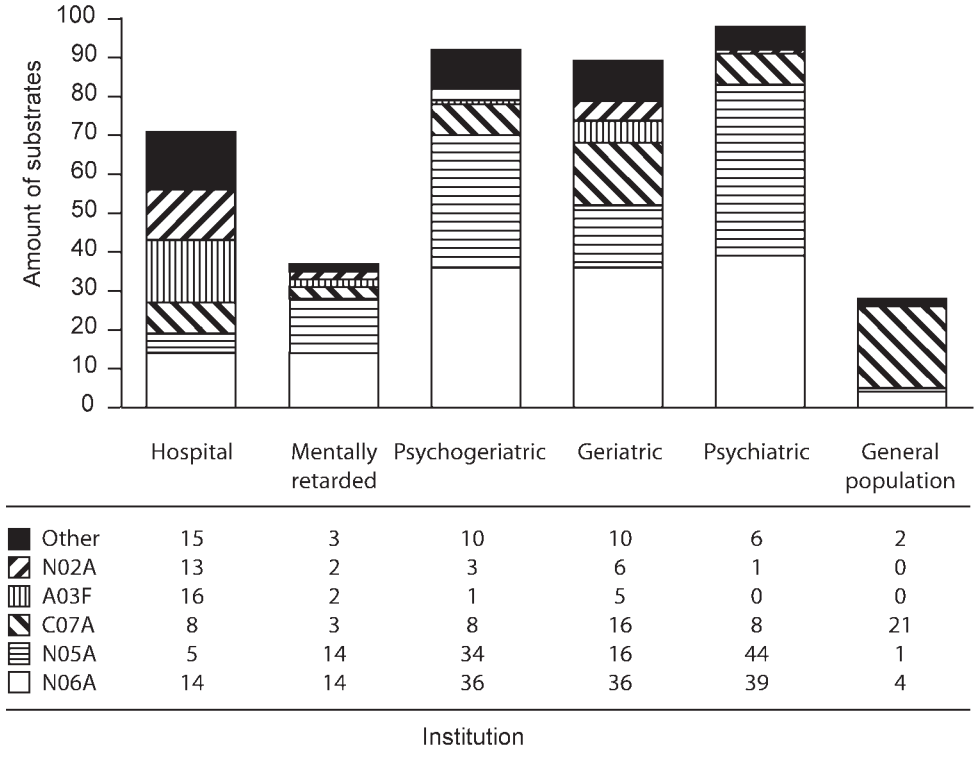

Figure 1. Amount (absolute numbers) of drugs metabolized by CYP2D6 classified by Anatomical Therapeutic Classification in different populations. N06A: amitriptyline (34[a]), clomipramine (19), fluoxetine (11), fluvoxamine (8), imipramine (1), nortriptyline (11), paroxetine (38), venlafaxine (21); N05A: aripiprazole (3), haloperidol (39), perphenazine (1), risperidone (71); C07A: carvedilol (9), metoprolol (45), nebivolol (1), propranolol (9); A03F: metoclopramide (24); N02A: tramadol (25); other: codeine (R05D)(16), flecainide (C01B)(4), tamoxifen (L02B)(7), timolol (S01E)(6), promethazine (R06A)(13). [a]Total number of prescriptions in the total population (N = 900)

genotyping in clinical practice. It is suggested that 20–30% of all drugs are metabolized by CYP2D6.[4,5] We found a lower proportion of the use of drugs metabolized by CYP2D6 in all patient populations, with the lowest proportion (7.0%) in the general hospital and the general population and the highest proportion (11.8%) in psychiatric patients. However, looking at the prevalence of patients treated with at least one drug metabolized by CYP2D6, we found a high prevalence in several populations, specifically, psychiatric, psychogeriatric, and geriatric patients who were at risk for treatment with at least one drug metabolized by CYP2D6 with a prevalence of approximately 50%. The NNG to find one patient with compromised metabolism by CYP2D6 who uses a drug metabolized by that isoenzyme at a specific moment was only 13. The NNG would probably be much lower if we could establish the lifetime risk, or even the one year risk, for treatment with a drug metabolized by CYP2D6.

We expected that mentally retarded patients and older patients would be treated frequently with drugs metabolized by CYP2D6 as well, but we could not support this hypothesis with our data. Apparently, specific patient populations admitted to particular institutions or wards are at risk for treatment with drugs metabolized by CYP2D6. Our study was not intended to provide evidence regarding the clinical relevance of CYP2D6 genotyping; it merely shows that if genotyping is relevant for patient care, the highest probability of cost-effectiveness will most likely be in these specific patient populations (ie, psychiatric, psychogeriatric, geriatric).

Drugs metabolized by CYP2D6 and prescribed in different populations were most frequently (62%) antidepressants (ATC N06A) and antipsychotics (ATC N05A). Some recently introduced psychotropic drugs are not primarily metabolized by CYP2D6 (eg, citalopram, sertraline, olanzapine, quetiapine). However, these data show that, despite the introduction of these drugs, CYP2D6 remains an important metabolizing enzyme in daily clinical practice. Additionally, it has been suggested that pharmaceutical industries are reluctant about the introduction of primary substrates for CYP2D6 because of proposed problems with drug interactions and the polymorphic metabolism.[4,23] Many companies will not continue to develop drug candidates metabolized by CYP2D6 unless they offer unique properties. This can result not only in decreased influence of CYP2D6 in the metabolism of drugs in the near future, but also the possible denial of potential effective drugs to patients.[24] However, although we do not know how many CYP2D6 substrates were withdrawn by pharmaceutical industries before they reached the market in 2005 and 2006, several psychotropic agents that are substrates for CYP2D6 (aripiprazole, duloxetine, atomoxetine) were introduced, suggesting that it will remain an important metabolizing enzyme for the near future.[25-27]

Conclusions

In our study, several populations had a high prevalence of patients who were treated with at least one drug metabolized by CYP2D6, with most of those drugs being antidepressants or antipsychotics. These findings suggest that populations treated with these drugs may benefit most from implementation of CYP2D6 genotyping.

Hans Mulder PharmD, Faculty of Science, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; Department of Clinical Pharmacy, Wilhelmina Hospital, Assen, Netherlands

Eibert R Heerdink PhD, Faculty of Science, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University

Elsje E van Iersel PharmD, Department of Clinical Pharmacy, Wilhelmina Hospital

Frederik W Wilmink MD PhD, Mental Health Services Drenthe, Assen

Antoine CG Egberts PhD, Professor of Clinical Pharmacoepidemiology, Faculty of Science, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University; Department of Clinical Pharmacy, University Medical Center, Utrecht

Reprints: Dr. Egberts, Faculty of Science, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3508 TB Utrecht, Netherlands, fax 31-30-2539166, A.C.G.Egberts@pharm.uu.nl

References

1. Wolf CR, Smith NL, Smith G. Pharmacogenetics. BMJ 2000:320;987-90.
2. Kirchheiner J, Fuhr U, Brockmoller J. Pharmacogenetics-based therapeutic recommendations—ready for clinical practice? Natl Rev Drug Discov 2005;4:639-47.
3. De Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics 2006;47:75-85.
4. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J 2005;5:6-13.
5. Gardiner SJ, Begg EJ. Pharmacogenetic testing for drug metabolizing enzymes: is it happening in practice? Pharmacogenet Genomics 2005; 15:365-9.
6. Tamminga WJ, Wemer J, Oosterhuis B, et al. Polymorphic drug metabolism (CYP2D6) and utilisation of psychotropic drugs in hospitalised psychiatric patients: a retrospective study. Eur J Clin Pharmacol 2003;59:57-64.
7. Davies SJ, Eayrs S, Pratt P, Lennard MS. Potential for drug interactions involving cytochromes P450 2D6 and 3A4 on general adult psychiatric and functional elderly psychiatric wards. Br J Clin Pharmacol 2004;57:464-72.
8. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 2004;9:442-3.
9. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 2000
10. Drug interaction table. Indiana University Department of Medicine. http://medicine.iupui.edu/flockhart/table.htm (accessed 2006 May 16).
11. Mulder H, Wilmink FW, Beumer TL, Tamminga WJ, Jedema JN, Egberts AC. The association between cytochrome P450 2D6 genotype and prescription patterns of antipsychotic and antidepressant drugs in hospitalized psychiatric patients: a retrospective follow-up study. J Clin Psychopharmacol 2005;25:188-91.
12. Brockmoller J, Kirchheiner J, Schmider J, et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.

13. Mulder H, Herder A, Wilmink FW, Tamminga WJ, Belitser SV, Egberts AC. 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. Pharmacoepidemiol Drug Saf 2006;15:107-14.
14. Bazire S. Psychotropic drug directory 2002. Bath, England: Mark Allen Publishing Ltd., 2001.
15. Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M. Metabolic drug interactions. Philadelphia, Lippincott Williams & Wilkins, 2000.
16. Genemedrix: drug–drug and drug-gene interaction software. www.genemedrx.com (accessed 2006 Dec 4).
17. Grasmader K, Verwohlt PL, Kuhn KU, et al. Population pharmacokinetic analysis of mirtazapine. Eur J Clin Pharmacol 2004;60:473-80.
18. Desta Z, Wu GM, Morocho AM, Flockhart DA. The gastroprokinetic and antiemetic drug metoclopramide is a substrate and inhibitor of cytochrome P450 2D6. Drug Metab Dispos 2002;30:336-43.
19. Nakamura K, Yokoi T, Inoue K, et al. CYP2D6 is the principal cytochrome P450 responsible for metabolism of the histamine H1 antagonist promethazine in human liver microsomes. Pharmacogenetics 1996;6:449-57.
20. Kirchheiner J, Henckel HB, Meineke I, Roots I, Brockmoller J. Impact of the CYP2D6 ultrarapid metabolizer genotype on mirtazapine pharmacokinetics and adverse events in healthy volunteers. J Clin Psychopharmacol 2004;24:647-52.
21. Jaanson P, Marandi T, Kiivet RA, et al. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology (Berl) 2002;162:67-73.
22. Brynne N, Dalen P, Alvan G, Bertilsson L, Gabrielsson J. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine. Clin Pharmacol Ther 1998;63:529-39.
23. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci 2004;25:193-200.
24. Ozdemir V, Kalow W, Tothfalusi L, Bertilsson L, Endrenyi L, Graham JE. Multigenic control of drug response and regulatory decision-making in pharmacogenomics: the need for an upper-bound estimate of genetic contributions. Curr Pharmacogenom 2005;3:53-71.
25. Dugan SE, Fuller MA. Duloxetine: a dual reuptake inhibitor. Ann Pharmacother 2004;38:2078-85. Epub 2 Nov 2004. DOI 10.1345/aph.1E084
26. Eiland LS, Guest AL. Atomoxetine treatment of attention-deficit/hyperactivity disorder. Ann Pharmacother 2004;38:86-90. DOI 10.1345/aph.1D144
27. Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. Ann Pharmacother 2003;37:687-94. DOI 10.1345/aph.1C297

EXTRACTO

INTRODUCCIÓN: A pesar del gran número de estudios que han investigado la relevancia clínica potencial del genotipado CYP2D6 en la prevención del fracaso terapéutico (ej, eficacia insuficiente y/o efectos adversos inaceptables), la prevalencia de pacientes que utilizan fármacos metabolizados por el CYP2D6 es relativamente desconocida.

OBJETIVO: Investigar la prevalencia de pacientes que utilizan fármacos metabolizados por el CYP2D6 en diferentes poblaciones de pacientes.

MÉTODOS: En este estudio cruzado se investigaron 6 poblaciones de pacientes diferentes: población general, población general hospitalizada, población geriátrica, psicogeriatrica, psiquiátrica y enfermos con retraso mental. De cada población, se seleccionaron aleatoriamente 150 pacientes adultos que utilizaban al menos un medicamento. Los resultados principales fueron la prevalencia de pacientes que utilizaban al menos un fármaco metabolizado por el CYP2D6. La prevalencia de pacientes que utilizaban al menos un sustrato CYP2D6 en diferentes poblaciones fue comparada con la población general utilizando la prueba estadística del χ^2. Los datos se expresaron como el riesgo relativo (RR) con un 95% de intervalo de confianza (95% IC).

RESULTADOS: Los pacientes procedentes de hospitalización (RR 1.81; 95% IC 1.26 y 2.62), los pacientes geriátricos (RR 2.16; 95% IC 1.26 y 2.62), los pacientes psicogeriatricos (RR 2.31; 95% IC 1.63 y 3.27), y los pacientes psiquiátricos (RR 2.44; 95% IC 1.73 y 3.44) fueron tratados mas frecuentemente con al menos un fármaco con metabolización por el CYP2D6 comparado con los pacientes en la población general. Aproximadamente el 50% de los pacientes psiquiátricos (52%), psicogeriatricos (49%), y geriátricos (46%) utilizaban al menos un fármaco metabolizado por el CYP2D6. En total, 416 fármacos metabolizados por el CYP2D6 fueron prescritos, siendo 257 (62%) de los fármacos clasificados como antidepresivos (ATC N06A) o antipsicóticos (ATC N05A).

CONCLUSIONES: Diversas poblaciones de pacientes (psiquiátricos, psicogeriatricos, geriátricos) presentan una alta prevalencia de tratamientos con al menos un medicamento metabolizado por el CYP2D6. Los fármacos metabolizados por el CYP2D6 fueron fundamentalmente antidepresivos o antipsicóticos (62%). Este estudio no proporciona evidencia sobre la relevancia clínica del genotipado CYP2D6, pero simplemente muestra que, si el genotipado CYP2D6 se considera relevante para el tratamiento de los pacientes, el mayor ratio de coste-efectividad se obtendra muy probablemente en poblaciones de pacientes específicas.

Corinne Zara Yahni

RÉSUMÉ

ÉTAT DES CONNAISSANCES: Bien que plusieurs études investiguent la pertinence clinique potentielle de déterminer le génotype du CYP2D6 pour prévenir un échec au traitement (ex, manque d'efficacité et/ou effets indésirables inacceptables), la prévalence des patients utilisant des médicaments métabolisés par le CYP2D6 est relativement peu connue.

OBJECTIF: Rechercher la prévalence des patients utilisant des médicaments métabolisés par le CYP2D6 dans différentes populations de patients.

MÉTHODOLOGIE: Dans cette étude transversale, 6 populations différentes de patients ont été investiguées: des patients de la population générale, des patients d'un hôpital général, des patients gériatriques, des patients psycho-gériatriques, des patients psychiatriques, et des patients ayant un retard mental. Dans chaque population, 150 patients adultes utilisant au moins un médicament ont été sélectionnés de façon aléatoire. L'objectif principal était de déterminer la prévalence des patients utilisant au moins un médicament métabolisé par le CYP2D6. La prévalence des patients utilisant au moins un substrat du CYP2D6 dans les différentes populations a été comparée à celle de la population générale en utilisant le test statistique du χ^2. Les données ont été exprimées sous forme de risque relatif (RR) et d'intervalle de confiance à 95% (IC 95%).

RÉSULTATS: Les patients de l'hôpital général (RR 1.81; IC 95% 1.26 à 2.62), les patients gériatriques (RR 2.16; IC 95% 1.26 à 2.62), les patients psycho-gériatriques (RR 2.31; IC 95% 1.63 à 3.27) et les patients psychiatriques (RR 2.44; IC 95% 1.73 à 3.44) ont été traités plus fréquemment avec au moins un médicament métabolisé par le CYP2D6 en comparaison des patients de la population générale. Approximativement 50% des patients psychiatriques (52%), psycho-gériatriques (49%) et gériatriques (46%) utilisaient au moins un médicament métabolisé par le CYP2D6. Au total, 416 médicaments métabolisés par le CYP2D6 ont été prescrits dont 257 (62%) de ces médicaments faisaient partie de la classe des antidépresseurs ou des antipsychotiques.

CONCLUSIONS: Une prévalence élevée de patients utilisant au moins un médicament métabolisé par le CYP2D6 a été retrouvée chez plusieurs populations de patients (psychiatriques, gériatriques et psycho-gériatriques). Les médicaments métabolisés par le CYP2D6 étaient principalement des antidépresseurs et des antipsychotiques. Cette étude ne témoigne pas de l'importance clinique de déterminer le génotype du CYP2D6 mais elle démontre simplement que si la détermination du génotype devient pertinente pour les soins du patient, il serait vraisemblablement plus coût efficace de l'effectuer chez des populations spécifiques de patients.

Marie Larouche