ORIGINAL RESEARCH ARTICLE

Drug Safety 2009; 32 (3): 255-264
0114-5916/09/0003-0255/$49.95/0

© 2009 Adis Data Information BV. All rights reserved.

Spontaneous ADR Reports as a Trigger for Pharmacogenetic Research

A Prospective Observational Study in the Netherlands

Eugène van Puijenbroek,[1] *Jean Conemans*[2] and *Kees van Grootheest*[1]

1 Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
2 Hospital Pharmacy ZANOB, 's-Hertogenbosch, the Netherlands

Abstract

Background: Information on genetic polymorphisms in drug-metabolizing enzymes is valuable when analysing the causal relationship between drug intake and an adverse drug reaction (ADR). Patients who have experienced an ADR should be informed about the possible existence of genetic polymorphisms that may contribute to the occurrence of ADRs, since this will allow adequate dosing of future medication.

In collaboration with the regional hospital pharmacy Ziekenhuisapotheek Noord-Oost-Brabant (ZANOB), the Netherlands Pharmacovigilance Centre Lareb developed a method for informing physicians or pharmacists and their patients about a possible pharmacogenetic involvement in the pathogenesis of the reported ADR and for offering easy access to genotyping if requested by the treating physician. An anonymized copy of the test results could be used for the interpretation of possible signals at the pharmacovigilance centre.

Objectives: The aim of this study was to gain insight into the feasibility of informing the reporting physician or pharmacist about possible involvement of a genetic polymorphism and subsequent genotyping of patients based on ADR reports received by the Netherlands Pharmacovigilance Centre.

Results: A total of 38 reports were selected in which genotyping was considered useful. In 15 of 38 cases (39.5%), the reporting health professionals actually initiated genotyping. The majority of the drugs implicated in causing ADRs were selective serotonin reuptake inhibitors, followed by other antidepressants and antipsychotic drugs. No logistical problems were encountered during this study.

Conclusion: The level of participating health professionals in genotyping their patients was relatively high. Apparently, reporting health professionals share the vision that information on pharmacogenetic characteristics of their individual patients is important. The use of an existing infrastructure for DNA sampling that is familiar to the patients and health professionals may have contributed to the high response rate.

Pharmacovigilance centres may suggest pharmacogenetic investigation and subsequent individualized pharmacogenetic counselling after a reported

ADR. These centres can also be a valuable starting point for pharmacogenetic studies, since data from different sources can be combined in the assessment of the causal relationship between drug intake and an ADR. This study shows that genotyping initiated by pharmacovigilance centres is indeed feasible, when using the standard laboratory testing infrastructure.

Background

Adverse drug reactions (ADRs) are responsible for considerable morbidity. A prospective study in the UK showed that ADRs are responsible for 6.5% of acute hospital admissions; the majority of the ADRs appeared to be avoidable. Knowledge of possible risk factors for developing ADRs in daily practice is of utmost importance. Although many of the drugs implicated have proven benefit, it is crucial to reduce the burden of ADRs and thereby further improve the benefit-to-harm ratio of the drugs.[1]

After marketing of a drug, not all ADRs and their risk factors are known. Pharmacovigilance, being the science dedicated to the safety of drugs as used in daily practice, generates knowledge on harmful effects of drugs, both at the individual and the population level. This knowledge will eventually be applied in clinical practice and thus lead to the safer use of drugs.[2]

One of the methods used in pharmacovigilance is 'spontaneous reporting'. Trained assessors review reports of suspected ADRs submitted to pharmacovigilance centres in order to evaluate the relationship between the reported ADRs and suspected drugs. Since the response to a drug varies between patients, special attention is paid to the presence of individual risk factors that may increase the susceptibility for specific ADRs. The occurrence of ADRs depends on various aspects, such as individual variations in pharmacokinetics and pharmacodynamics, co-morbidity and other factors that may modify the occurrence and severity of ADRs. Analysis of these individual risk factors is needed to gain insight into the pathophysiology of the reported ADRs, but also to reduce the risk of ADRs in the individual patient in the future. One of the individual factors that may modify the pharmacokinetic characteristics of a drug is genomic variation in the cytochrome P450 (CYP) enzyme family, which may induce or inhibit the phase I metabolism of specific drugs. In a systematic literature review by Phillips et al.,[3] 27 drugs frequently cited in ADR studies were identified. Among these drugs, 59% were metabolized by at least one enzyme of which variant alleles leading to a decreased metabolism rate exist. Of randomly selected drugs, this genetic variability ranged from 7% to 22%. The authors suggested that drug therapy based on individual patient genetic make-up may result in a clinically important reduction in adverse outcomes.[3]

In recent years there has been a growing awareness of the influence of genetic polymorphisms on susceptibility to ADRs.[3] Patients can be genotyped to determine their pharmacogenetic characteristics in order to reduce their chances of experiencing ADRs again in the future. Unfortunately, the possibility of a genetic involvement is often not recognized by the reporting physician or pharmacist and therefore not used in the context of daily clinical routine.[4]

For pharmacovigilance centres, information on the presence of polymorphisms in genes encoding drug-metabolizing enzymes provides a valuable contribution in the analysis of the causal relationship between the suspected drug and the ADR. In addition, the individual patient should be informed about the existence of genetic polymorphisms that influence the occurrence of the ADR, so that future treatment with drugs metabolized by the enzyme involved can be administered at an appropriate dose. This information may be part of the regular feedback provided to the reporting physicians and pharmacists by the pharmacovigilance centre.

© 2009 Adis Data Information BV. All rights reserved.

In collaboration with the Hospital Pharmacy Ziekenhuisapotheek Noord-oost-Brabant (ZANOB), the Netherlands Pharmacovigilance Centre Lareb developed a strategy for identifying cases in which pharmacogenetic involvement in the occurrence of the ADR is suspected, informing the treating physician and pharmacist and genotyping patients if requested. The goal of this procedure is to inform reporting physicians and pharmacists about the possibility of a genetic polymorphism and offer them access to a specialized laboratory. An anonymized copy of the test results can be used for interpretation purposes at the pharmacovigilance centre.

The aim of this study was to gain insight into the feasibility of informing the reporting physician or pharmacist and subsequent genotyping of patients based on ADR reports received by the Netherlands Pharmacovigilance Centre.

Methods

Study Population

The Netherlands Pharmacovigilance Centre Lareb maintains the Spontaneous Reporting System in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Each year Lareb receives approximately 6000 reports on possible ADRs, provided by healthcare professionals, patients and the Marketing Authorization Holders of drugs approved for marketing in the Netherlands. Reports contain information about the patient (i.e. age, sex), one or more suspected ADRs, medication used at the time of the event (both suspected and concomitant drugs), reporting source (physician, pharmacist or patient) and the year of reporting. Each report is evaluated by a trained assessor (either a physician or pharmacist) and filed in a database. When needed for an adequate assessment of the reports, additional follow-up information is requested. ADRs are coded according to the Medical Dictionary for Regulatory Activities terminology (MedDRA);[5] the drugs are classified according to the Anatomical Therapeutical Chemical (ATC) classification system.[6] Reporting health professionals always receive custom-made feedback on their reports.

The analysis of individual risk factors in pharmacovigilance centres relies on detailed clinical and pharmacological information provided by the reporter. In the Netherlands, every patient has his/her own pharmacy where information concerning drug use is filed in the Pharmacy Information System. Reports submitted by pharmacists include a complete overview of suspected and concomitant medication; reports submitted by physicians also contain information about current drug use.

To analyse potential drug interactions, the Netherlands Pharmacovigilance Centre developed software that incorporates information about the drug metabolism by the CYP system. The software provides instant information to the assessor about the phase I metabolism of the reported suspected and concomitant drugs in terms of the presence of substrates of the various CYP enzymes and drugs that may induce or inhibit them. This information enables the assessor to consider the existence of drug-drug interactions, but it may also point to the possibility of an aberrant metabolism of the reported drug.

Definitions

In this prospective observational study we analysed reports submitted to the Netherlands Pharmacovigilance Centre between 1 January 2004 and 1 January 2006. No control patients were selected. Reports were included when the suspected or interacting medication was a substrate of CYP2D6, CYP2C19 or CYP2C9 as indicated by a dedicated computer program, using the information provided by the Flockhart CYP drug interaction table as published on the Internet.[7] This programme links the suspected medication with information about substrates of the various CYP isoenzymes and thus enables an automated warning system.

Reports were included if there was a strong suspicion of the possible involvement of a polymorphism by the assessor. Reports were excluded in the event of the death of the patient involved, allergic reactions (a genetic involvement in the pathogenesis is unlikely in the event of an allergic reaction) and the likelihood of encountering

© 2009 Adis Data Information BV. All rights reserved.

logistical problems in taking blood samples and genotyping.

After identification of an eligible case by the assessor, a feedback letter with additional information about the study and procedure, together with the laboratory forms, were sent to the reporter. This procedure is in line with the existing procedure for providing feedback to healthcare professionals in our centre.

These laboratory forms were marked with the Lareb report number to enable linkage of the results of the genotyping with anonymous reports. In the event the reporter was a pharmacist, they were asked to forward the feedback letter and forms to the physician of the patient involved.

Information about a possible polymorphism should primarily serve patient care. The decision to have the patients tested was made by the treating physicians as part of their normal clinical routines. Blood samples were taken in the local laboratory of the patient, after which the samples were sent to the laboratory where the actual genotyping was carried out (Molecular Diagnostics, Hospital Pharmacy ZANOB, 's-Hertogenbosch, the Netherlands).

Genotyping

Genotyping was done on DNA isolated from 80 μL whole blood (EDTA) samples with a Generation Capture Column Kit (Gentra Systems Inc, Minneapolis, MN, USA) according to the manufacturer's instructions. The presence of the non-functional alleles 2D6*3, *4, *6 and *7 and the non-functional deletion allele 2D6*5 was determined as described by Steen et al.[8] The presence of the 2D6 gene duplication was analysed using the Cyp-17/Cyp-32 assay as described by Lovlie et al.[9] The presence of the decreased functional 2D6*9, *10 and *41 alleles was determined by real-time polymerase chain reaction using Applied Biosystems Drug Metabolizing Enzyme assays C__32407229_60, C__11484460_40 and C__34816116_20, respectively. The CYP2C19*2 allele and the CYP2C9*2 and *3 alleles were analysed as described by de Morais et al.,[10] Steward et al.[11] and Sullivan-Klose et al.,[12] respectively.

After genotyping, the results were sent by the laboratory to the patient's physician. Information provided by the laboratory comprised an explanation of possible consequences of the findings, i.e. whether the patient was a slow or rapid metabolizer. In addition, a list of drugs that are metabolized by the aberrant metabolism and may therefore cause problems in the future was provided. A copy of the results with detailed information on the consequences of the findings and a list of drugs that may cause harm in the future was also sent to the patient. Finally, an anonymized copy of the results was sent to the Netherlands Pharmacovigilance Centre Lareb to be completed with the original report. The flow of information is shown in figure 1.

At the Netherlands Pharmacovigilance Centre, information was collected concerning age and sex of the patient, suspected drug and reported ADR, the seriousness of the reaction, the type of genotyping requested by the Netherlands Pharmacovigilance Centre, and the outcome of the genotyping. Remarks or suggestions regarding the procedure from health professionals or patients were noted.

Statistical Analysis

When appropriate, statistical analysis was conducted using the software package SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 38 reports were selected in which genotyping was considered to be useful. The primary source of these reports was a physician in 23 cases (10 general practitioners [GPs] and 13 specialist doctors) and a pharmacist in 15 cases. Genotyping of 2D6 was requested 27 times, 2C9 four times and genotyping of 2C19 was asked for in seven cases.

An overview of the eligible cases and the outcome of the analyses are shown in figure 2. Actual genotyping was carried out in 15 of 38 cases (39.5%). Pharmacists, especially, tended to initiate additional genotyping, although the difference between pharmacists and physicians was

© 2009 Adis Data Information BV. All rights reserved.

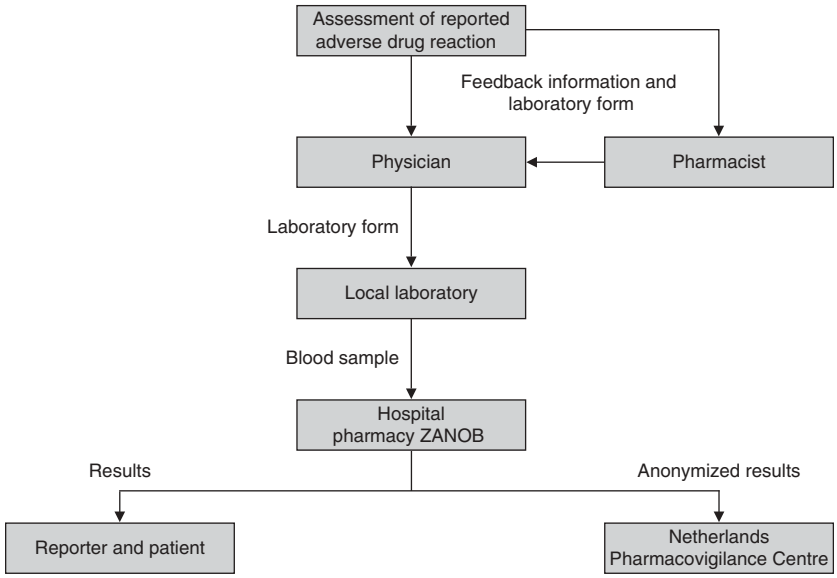

Fig. 1. Flow of information for investigating genetic factors in the pathogenesis of reported adverse drug reactions to the Netherlands Pharmacovigilance Centre.

not statistically significant (Pearson χ^2 two-sided $p = 0.553$).

Of the 38 reports in which genotyping was requested, 15 were considered to be serious ADRs according to internationally accepted criteria.[13] Of the latter reports, in one report the described ADR was considered to be life-threatening (torsade de pointes), five reported ADRs were responsible for hospital admission and nine reports were labelled as an 'other medically important condition' by the reporter.

The majority of the suspected drugs for which genotyping was requested by the Netherlands Pharmacovigilance Centre Lareb were selective serotonin reuptake inhibitors (n = 15), followed by, amongst others, antidepressants (n = 5) and antipsychotic drugs (n = 3). In the majority of cases, the reported ADRs belonged to the MedDRA System Organ Class (SOC) 'nervous system disorders' (n = 20). Also, a relatively large number of reported cases belonged to the SOC 'psychiatric disorders' (n = 9). Details of the cases in which genotyping actually took place and those cases in which additional analysis did not take place are shown in tables I and II, respectively.

An overview of the 15 reports for which the analysis was carried out is provided in table III. For 2D6, the phenotype was expressed as 'intermediate', 'slow metabolizer' or 'ultrarapid metabolizer' according to the recommendations of the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy.[14] Of the 15 (38.5%) patients who were genotyped, nine were suspected of a possible polymorphism of CYP 2D6, four of 2C19 and two patients of 2C9.

A total number of eight variants were detected. For CYP2D6, four patients were found to carry a non-functional allele, one patient carried a decreased functional (2D6*41) allele together with a deletion allele (2D6*5), and one patient carried a functional duplication allele. With regard to CYP2C19, one patient had one functional allele for 2C19 and one patient had no allele for 2C19. In CYP2C9, no variations were found (see table III).

No patients had to be excluded because of possible logistical problems, nor were any problems encountered during the study. One patient pointed out the possibility that although genotyping was reimbursed, patients may have to deal

© 2009 Adis Data Information BV. All rights reserved.

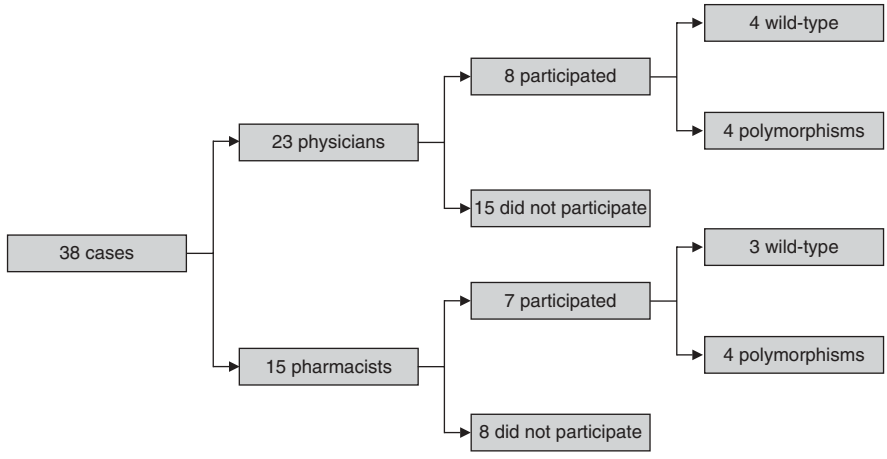

Fig. 2. Cases eligible for participation in the study and outcomes.

with the policy excess of the health insurance. No other remarks have been received.

Discussion

The accumulating knowledge of human genomic variation can be used for the development of personalized medicine, which aims at increasing the efficacy of drug treatment and decreasing the number of ADRs.[15]

Pharmacovigilance centres can play an important role in the recognition of pharmacogenetic elements in problems with medication, and in subsequently suggesting personalized medicine. A key element of the science of pharmacovigilance is providing adequate feedback to the reporting health professionals and patients.[2] Although assessors at pharmacovigilance centres do not have a formal role in the treatment of the individual patient, health professionals and patients should be informed the moment a possible risk factor is identified by the pharmacovigilance centres. Pharmacovigilance centres may therefore operate in a more bidirectional manner. In addition to collecting data, providing feedback will become more important. This contributes to the improvement of individual patient care.

Assessors of a pharmacovigilance centre may suspect a possible pharmacogenetic involvement, but the decisions regarding whether or not to have the patient genotyped should be made by the treating physician. Based on the information provided by the reporters, a reliable selection cannot be made by the pharmacovigilance centre itself. The role for the pharmacovigilance centre is to make the reporter aware of the fact that genetic factors may play a role in the occurrence of the ADR. It is up to the physician to decide if additional testing should take place. In the event of reporting of an ADR by a pharmacist, the treating physician was asked if genotyping was considered necessary. Since the role of the pharmacovigilance centre is restricted to providing information about the possible role of a pharmacogenetic factor, no strict criteria were in place to select possible candidates for genetic testing.

The goal of this study was to gain insight into the feasibility of genotyping patients based on reports received by the Netherlands Pharmacovigilance Centre. From the perspective of the pharmacovigilance centre, this information is beneficial in identifying possible risk factors for developing ADRs. The proportion of cases in which additional genotyping was carried out was 39.5%. Apparently, reporting health professionals share the vision that information on pharmacogenetic characteristics of the individual patients is important. Consequences for

© 2009 Adis Data Information BV. All rights reserved.

future pharmacotherapy in the individual patients may have contributed to this relatively high response.

Cases were selected on partly subjective grounds. Although there were hardly any exclusion criteria for the selection of cases in which genetic polymorphisms might have played a role, the actual number of cases selected by the assessors was still rather low. We would expect that the number of selected cases would increase when this approach is incorporated into the daily routine of this pharmacovigilance centre.

In a pilot study of the New Zealand Intensive Medicines Monitoring Programme, a nested case-control design was used to investigate whether patients with genetic variants in P-glycoprotein and CYP2C9 were more susceptible to psychiatric or visual disturbances following cyclooxygenase-2 inhibitor use than matched control patients. In this study, 18 patients (37 cases and 91 controls) were contacted by mail and were asked to contact their GP so that a buccal swab could be taken. Genotyping was carried out in 15 (41%) cases and 24 (26%) control patients.[16] Previous experiences by the same group, using DNA extracted from blood samples, yielded a very low number of patients willing to participate.[17] The authors concluded that another method of collecting DNA would probably yield higher results, and suggested using a buccal swab.[16] In a feasibility study into drug-induced arrhythmias to proarrhythmic drugs, using the database of the Netherlands Pharmacovigilance Centre, De Bruin et al.[18] used data from a spontaneous reporting system to recruit patients as well as controls. Patients were asked to fill in a questionnaire and to provide a buccal swab DNA sample through the mail. From the 45 eligible cases, four cases and five matched controls could be included, giving an overall participation rate of 9%. The main reason for GPs not participating was a lack of time.[18] In the present study in which the same database was used, the level of participation was considerably higher (39.5%).

Table I. Overview of reports (n = 15) on which analysis was carried out

Suspected drug and daily dose if known (mg)	Patient sex and age (y)	Reported ADR	Analysis	Outcome	Remarks
Flecainide 200	F, 64	Arrhythmia	2D6	w/*4	
Mirtazapine 30	M, 32	Convulsions, aggressiveness	2D6	*5/*41	
Rabeprazole 20	M, 57	Nephritis interstitial	2C19	w/w	
Citalopram 20	F, unknown	Convulsions (petit mal?)	2C19	w/w	
Montelukast 10	M, 47	Gastrointestinal tract bleeding	2C9	w/w	
Venlafaxine 75	F, 48	Haematoma	2D6	w/*4	
Celexocib 100	F, 32	Weight increase	2C9	w/w	Positive rechallenge
Mirtazapine 15	M, 29	Hepatic enzymes increased, appetite increased, fatigue	2D6	w/w	
Tolterodine 2	F, 58	Diplopia	2D6	w/w	
Citalopram 20	M, 41	Parkinsonism	2C19	*2/*2	
Galantamine 8 twice daily	F, 71	Depression aggravated	2D6	Dup w/w	
Dextromethorphan, fluoxetine	M, 37	Serotonin syndrome	2D6	w/w	
Fluoxetine	F, 13	Mydriasis, orthostatic hypotension, sleep disorder	2D6	w/*4	
Acenocoumarol, ketoconazole	M, 57	Drug interaction, INR increased	2C19	w/*2	Additional factor for drug-drug interaction?
Haloperidol	M, 47	Apathy	2D6	w/*4	

ADR = adverse drug reaction; **F** = female; **INR** = International Normalized Ratio; **M** = male; **w** = wild type.

© 2009 Adis Data Information BV. All rights reserved.

It is possible that using the existing infrastructure for laboratory testing instead of asking patients to provide their own sample in the form of a buccal swab, might have increased the level of participation. In the study by Clark et al.,[16] in which buccal swabs were taken by the GPs of the patients involved, a similar level of participation was found as in our study. This supports the idea that DNA sampling should preferably be carried out using an infrastructure that is familiar to the patients and health professionals involved. The way DNA samples are collected, either blood samples or buccal swabs, is probably less important.

No logistical problems were encountered using the approach described in this article. The method of working did not interfere with the daily routine of health professionals in the Netherlands and the genotyping procedure was in line with the normal way of laboratory testing in our country. Currently, a limited number of laboratories offer the opportunity for genotyping. For this reason, transport of blood samples between the various laboratories and the laboratory where the genotyping was performed was needed. It is expected that the number of laboratories in which genotyping can be carried out will increase over the next years, so that the procedure can be simplified

Table II. Overview of reports (n = 23) on which analysis was not carried out

Suspected drug and daily dose if known (mg)	Patient sex and age (y)	Reported ADR	Proposed analysis	Remarks
Ranitidine 20 Paroxetine 20	M, 14	Involuntary movements, tremor	2D6	Paroxetine is a substrate of 2D6, which is inhibited by ranitidine. Additional factor?
Risperidone 0.5	M, 12	QTc interval prolongation	2D6	
Metoclopramide, midazolam, atropine	F, 75	Torsade de pointes	2D6	2D6 because of metabolism metoclopramide
Glimepiride	F, 49	Paraesthesia	2C9	Positive rechallenge
Metoclopramide 20, paroxetine 20	F, 38	Extrapyramidal disorder	2D6	Additional factor for drug-drug interaction?
Imipramine 150	F, 51	Epilepsy temporal lobe	2D6	
Montelukast 5	M, 3	Abnormal behaviour	2C9	
Metoclopramide 20	F, 49	Torticollis, trismus	2D6	
Risperidone 1	F, 39	Muscle rigidity	2D6	
Paroxetine	F, 37	Paraesthesia	2D6	
Citalopram	F, 31	Galactorrhoea	2C19	
Fluoxetine	F, 31	Haematoma	2D6	
Escitalopram	F, 51	Depressed level of consciousness	2C19	
Paroxetine	M, 36	Convulsion	2D6	
Phenprocoumon, venlafaxine	F, 76	Haematuria	2D6	
Paroxetine	F, 33	Parkinsonism	2D6	
Dextromethorphan	M, 56	Hallucination	2D6	
Aripiprazole	F, 24	Akathisia, dyskinesia	2D6	
Venlafaxine	F, 30	Hypertension	2D6	
Tolterodine	F, 57	Visual disturbance	2D6	
Moclobemide	F, 53	Accommodation disorder, visual acuity reduced	2C19	
Atomoxetine	M, 12	Aggression	2D6	
Atomoxetine	F, 18	Aggression	2D6	

ADR = adverse drug reaction; **F** = female; **M** = male.

© 2009 Adis Data Information BV. All rights reserved.

Table III. Results of genotyping 2D6, 2C19 and 2C9

Genotype	2D6	2C19	2C9
Wild type/wild type	3	2	2
Duplication of wild-type allele	1		
Intermediate metabolizer (2D6) or heterozygote (2C19)	4	1	
Slow metabolizer (2D6) or homozygote (2C19)	1	1	
Total	9	4	2

and the time needed for the analysis can be shortened.

Reporting pharmacists cannot request laboratory testing themselves; they had to refer the patient to the treating physician. There appeared to be no difference between the number of physicians and pharmacists participating in this project. The relative number of pharmacists even slightly outnumbered the number of physicians, although the difference was not statistically significant.

In the study, genotyping was reimbursed through health insurance, provided that a physician made the request. As the rules regarding reimbursement may vary from patient to patient, in the feedback letter to pharmacists and physicians the reimbursement rules regarding health insurance were clearly explained.

Eight of fifteen samples were shown to carry a genetic polymorphism in one of the three studied (relevant) CYP450 genes. Although the number of patients who were actually genotyped in this study is too low to draw any firm conclusions, the number of polymorphisms showed a tendency to be over-represented compared with the general population.

It is well known that the number of polymorphisms of the CYP system is higher within ethnic backgrounds other than Caucasian. On the forms used for ADR reporting in the Netherlands no information about the ethnic background of the patient was asked for, so this could not be taken into account in the present study.

In their overview article about therapeutic drug monitoring and pharmacogenetic testing in pharmacovigilance, Jaquenoud et al.[4] called for the development of databases on drug-drug interactions and the impact of pharmacogenetic polymorphisms and ADR information systems to guide clinicians in individualized pharmacotherapy.[4] Taking into account the fact that concomitant medication is not always known and the use of over-the-counter drugs is not always reported, the possible involvement of the CYP system in drug-drug interactions is a point of concern. Monitoring for CYP involvement, for instance by automated linkage of databases concerning information of the CYP system, may enable a more active approach in pharmacovigilance and provide adequate feedback to the reporting physicians involved. Our study showed that pharmacovigilance centres may very well fulfil this role.

Conclusion

The level of participating health professionals in genotyping their patients was relatively high. Apparently, reporting health professionals share the vision that information on pharmacogenetic characteristics of their individual patients is important. The use of an existing infrastructure for DNA sampling that is familiar to the patients and health professionals may have contributed to the high response rate.

Pharmacovigilance centres may suggest pharmacogenetic investigation and subsequent individualized pharmacogenetic counselling after a reported ADR. These centres can also be a valuable starting point for pharmacogenetic studies, since data from different sources can be combined in the assessment of the causal relationship of drug intake and ADR. This study shows that genotyping initiated by pharmacovigilance centres is indeed feasible, when using the standard laboratory testing infrastructure.

Acknowledgements

No funding was provided to assist in the preparation of this study. Two major health insurance companies were informed and gave their approval. The investigators who conducted this study were employed by the Netherlands Pharmacovigilance Centre Lareb and the Hospital Pharmacy ZANOB (Ziekenhuisapotheek Noord-oost-Brabant). This study was performed as part of their regular work schedule.

© 2009 Adis Data Information BV. All rights reserved.

The authors have no conflict of interest related to the content of this study to declare.

References

1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329 (7456): 15-9
2. van Grootheest AC. Improving pharmacovigilance and the role of the pharmacist [thesis]. Groningen: Rijksuniversiteit Groningen, 2003
3. Phillips KA, Veenstra DL, Oren E, et al. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA 2001; 286 (18): 2270-79
4. Jaquenoud SE, van der Velden JW, Rentsch K, et al. Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. Drug Saf 2006; 29 (9): 735-68
5. MedDRA. MedDRA and MSSO website 2007 [online]. Available from URL: http://www.meddramsso.com/MSSOWeb/index.htm [Accessed 2007 Dec 1]
6. WHO Collaborating Centre for Drug Statistics Methodology. WHO Collaborating Centre for Drug Statistics Methodology 2007 [online]. Available from URL: http://www.whocc.no/atcddd/ [Accessed 2007 Dec 1]
7. Flockhart DA. Drug interactions: cytochrome P450 system [online]. Available from URL: http://medicine iupui edu/flockhart/2007 [Accessed 2007 Dec 1]
8. Steen VM, Andreassen OA, Daly AK, et al. Detection of the poor metabolizer-associated CYP2D6(D) gene deletion allele by long-PCR technology. Pharmacogenetics 1995; 5 (4): 215-23
9. Lovlie R, Daly AK, Molven A, et al. Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. FEBS Lett 1996; 392 (1): 30-4
10. de Morais SM, Wilkinson GR, Blaisdell J, et al. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem 1994; 269 (22): 15419-422
11. Steward DJ, Haining RL, Henne KR, et al. Genetic association between sensitivity to warfarin and expression of CYP2C9*3. Pharmacogenetics 1997; 7 (5): 361-67
12. Sullivan-Klose TH, Ghanayem BI, Bell DA, et al. The role of the CYP2C9-Leu359 allelic variant in the tolbutamide polymorphism. Pharmacogenetics 1996; 6 (4): 341-49
13. European Commission. Pharmacovigilance for medicinal products for human use volume 9A (version September 2008) [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf [Accessed 2009 Feb 12]
14. Swen JJ, Wilting I, de Goede AL, et al. Pharmacogenetics: from bench to byte. Clin Pharmacol Ther 2008; 83 (5): 781-7
15. Ingelman-Sundberg M. Pharmacogenomic biomarkers for prediction of severe adverse drug reactions. N Engl J Med 2008; 358 (6): 637-9
16. Clark DW, Donnelly E, Coulter DM, et al. Linking pharmacovigilance with pharmacogenetics. Drug Saf 2004; 27 (15): 1171-84
17. Clark DW, Morgan A, Hananeia L. Drug metabolism genotypes and their associations with adverse drug reactions in selected populations: a pilot study of methodology. Pharmacoepidemiol Drug Saf 2000; 9 (393): 400
18. De Bruin ML, van Puijenbroek EP, Bracke M, et al. Pharmacogenetics of drug-induced arrhythmias: a feasibility study using spontaneous adverse drug reactions reporting data. Pharmacoepidemiol Drug Saf 2006; 15 (2): 99-105

Correspondence: Dr *E.P. van Puijenbroek*, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, the Netherlands.
E-mail: e.vanpuijenbroek@lareb.nl

© 2009 Adis Data Information BV. All rights reserved.