Alimentary Pharmacology & Therapeutics

Review article: the prevalence and clinical relevance of cytochrome P450 polymorphisms

P. A. H. M. WIJNEN*, R. A. M. OP DEN BUIJSCH*, M. DRENT†, P. M. J. C. KUIPERS‡, C. NEEF§, A. BAST¶, O. BEKERS* & G. H. KOEK**

Departments of *Clinical Chemistry, †Respiratory Medicine, ‡Cardiology and §Pharmacology and Toxicology, University Hospital Maastricht, Maastricht, The Netherlands; ¶Department of Pharmacology and Toxicology, University Maastricht, Maastricht, The Netherlands; **Division of Gastroenterology/Hepatology, Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands

Correspondence to:
Dr G. H. Koek, Division of Gastroenterology/Hepatology, Department of Internal Medicine, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands.
E-mail: gkoe@sint.azm.nl

Conflicts of interest:
The authors have declared no conflicts of interest.

This article appeared as part of a supplement sponsored by Nycomed bv.

Publication data
Accepted 26 August 2007

SUMMARY

Background
Most drugs currently used in clinical practice are effective in only 25% to 60% of patients, while adverse drug reactions (ADRs) as a consequence of treatment are estimated to cost billions of US dollars and tens of thousands of deaths.

Aim
To review the prevalence and clinical significance of cytochrome P450 polymorphisms.

Results
The cytochrome P450 enzyme families 1–3 are responsible for 70 to 80% of all phase I dependent drug metabolisms. In 90% metabolic activity dependents on six enzymes: CYP1A2, CYP3A, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. Polymorphisms in the CYP450 gene can influence metabolic activity of the subsequent enzymes. A poor metabolizer (PM) has no or very poor enzyme activity. A consequence of PM is drug toxicity if no other metabolic route is available, or when multiple drugs are metabolized by the same cytochrome. In that case dose reduction is an option to prevent toxic effects.

Conclusions
In the future genotyping should be considered to identify patients who might be at risk of severe toxic responses, in order to guide appropriate individual dosage. Medical therapy should be a close cooperation between clinicians, pharmacologists and laboratory specialists, leading to reduced therapeutic errors, ADRs and health care costs.

Aliment Pharmacol Ther **26** (Suppl 2), 211–219

doi:10.1111/j.1365-2036.2007.03490.x

INTRODUCTION

The success of modern medicine is partly the result of effective medical treatment. Although the overall advantage of many drugs outweighs the side effects, substantial costs are still made due to the complications of drug therapy. Adverse drug reactions (ADRs) account for 8.2% hospital admissions in the Netherlands, four times more often in elderly persons. An estimated calculation showed that about 430 million euros could be saved each year when side effects are reduced.[1] More recently an observational study was performed in 21 different Dutch hospitals which showed that 2.4% of hospitalizations were the result of ADRs. Calculations showed that 85 million Euros could be saved when these ADRs were prevented (http://www.nvza.nl; Hospital Admissions Related to Medication study).

In the United States, as many as 3% of the hospitalizations per year are for reasons of drug–drug interactions.[2] ADRs are the fourth to sixth leading cause of death and direct hospital costs are between 1.56 and 4 billion dollars.[3] Pirmohamed *et al.*[4] analysed 18 820 hospitalizations in the United Kingdom (UK) in 2004 and found a correlation in 1225 cases between ADRs and the use of drugs like acetylic acid, diuretics, warfarin and non-steroidal anti-inflammatory drugs. By extrapolating these numbers Hitchen[5] reported that ADRs are the cause of 250 000 hospitalizations per year in the UK. Thus, drug interactions have become an important preventable iatrogenic complication and therefore knowledge of drug metabolisms is a prerequisite to prevent ADRs. The variability in drug response among patients is multi-factorial, including extrinsic factors like environmental aspects and also genetic and intrinsic factors that affect the disposition (absorption, distribution, metabolism and excretion) of a certain drug (Table 1). The existence of large population differences with small intra-patient variability is consistent with inheritance as determinant of drug response; it is estimated that genetics can account for 20–95% of variability in drug disposition and effects.[6] Two metabolization routes (phase I and phase II reactions) in the liver are responsible for the transformation of the majority of the clinically used medication. Phase I reactions, performed mainly by cytochrome P450 enzymes, involve hydroxylation, reduction and oxidation while in phase II reactions glucuronidation, sulfation, acetylation or methylation take place (Figure 1). These processes enhance the polarity or water solubility of the resulting metabolites, thus facilitating their removal through urine or bile. With the widespread possibility of determining the genetic profile of the cytochrome P450 enzymes, the metabolic capacity can be determined. Patients can be divided into ultra extensive (UEM), extensive (EM), intermediate (IM) or poor metabolizers (PM).[7] Important cytochrome P450 enzymes for drug metabolism are 1A2, 2C9, 2C19 and 2D6. This review will focus on the clinical relevance and prevalence of cytochrome P450 polymorphisms that are important in metabolism of many clinically used drugs.

CYTOCHROME P450 ENZYMES

The completion of the sequence of the human genome revealed the presence of 115 human CYP genes: 57 active and 58 pseudo-genes[8] which are summarized at the website http://drnelson.utmem.edu/cytochromeP450.html. An overview regarding some relevant Internet sites about cytochrome P450 enzymes is shown in Table 2. The cytochrome P450 enzymes are

Table 1. Scheme of drug metabolism

Extrinsic factors	Environment	Smoking
		Diet
		Alcohol
	Drug interactions	Prescribed drugs
		Over-the-counter drugs
		Herbal supplements
Intrinsic factors	Demographic	Gender
		Age
		Race
	Disease	Disturbed kidney excretion function
		Diminished liver blood perfusion
		Changed metabolic function
Genetic factors	Polymorphisms in genes encoding metabolic enzymes	

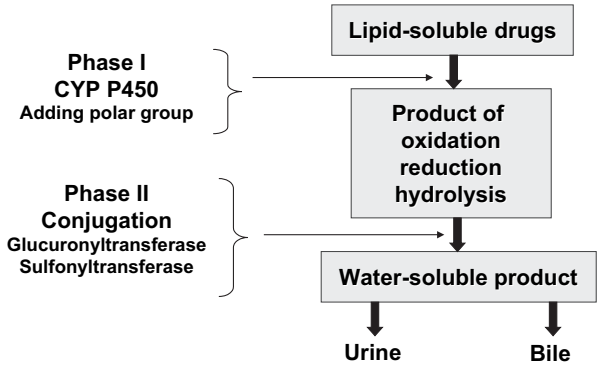

Figure 1. Most metabolic biotransformations occur at some point between absorption of the drug into the general circulation and its renal elimination. A few transformations occur in the intestinal lumen or intestinal wall. In general, all these reactions can be assigned to one of two major categories called phase I and phase II reactions.

a superfamily of haemoproteins that are the terminal oxidases of the mixed function oxidase system found on the membrane of the smooth endoplasmic reticulum preferentially expressed in the centrilobular area of the liver.[9]

Explanation of the term cytochrome P450 is: cyto stands for microsomal vesicles, chrome for coloured, P for pigmented and 450 for the 450 nanometer spectrophometric absorption peak.[10] Cytochrome P450 proteins are conveniently arranged into families and subfamilies on the basis of percentage amino acid sequence identity;[11–16] ≥40% identity on amino acid level is required for being in the same family, a letter indicating the subfamily ≥55% amino acid sequence identity and a number for the gene. Figure 2 illustrates an example of the cytochrome P450 enzyme nomenclature. The cytochrome P450 isoenzymes in families 1–3 are responsible for 70–80% of all phase I-dependent metabolism of clinically used drugs[17–19] and participate also in the metabolism of a large number of xenobiotic chemicals.

Substances (medicines or other compounds) that are metabolized by cytochrome P450 enzymes are called substrates. Some substances can inhibit the action of a cytochrome (so-called inhibitors), for example naringin in grapefruit which inhibits CYP3A4, while other substances (so-called inducers) can enhance the metabolism of a specific cytochrome P450 enzyme, for example smoking induces the action of CYP1A2.

Table 2. Useful Internet sites in cytochrome P450 research (accessed 1 August 2007)

Site	Address	Information
Human CYP allele nomenclature homepage	http://www.imm.ki.se/CYPalleles/	Latest update regarding new allelic variants of human cytochrome P450 isoenzymes with links to relevant references
Nelson's home page	http://drnelson.utmem.edu/cytochromeP450.html	All cytochrome P450 isoforms in human and other species
Cytochrome P450 substrates	http://medicine.iupui.edu/flockhart	Latest update about cytochrome P450 substrates, inducers and inhibitors
Cytochrome P450 database	http://cpd.ibmh.msk.su/	Relevant collection of cytochrome P450 nomenclature, structure and properties
GENTEST's human cytochrome P450 metabolism database	http://www.genotest.com/human_p450_database/index.html	Human cytochrome P450 metabolism organized according to enzyme, therapeutic area, etc.
Pharmacogenetics and pharmacogenomics database	http://www.pharmgkb.org/index.jsp	Relevant site with lots of information of the enzymes and transporters involved in drug metabolism
Drug–drug and drug–gene interaction software	http://www.genemedrx.com/	Software package that helps doctors/researchers to treat patients more efficiently by avoiding drug–drug and drug–gene interactions

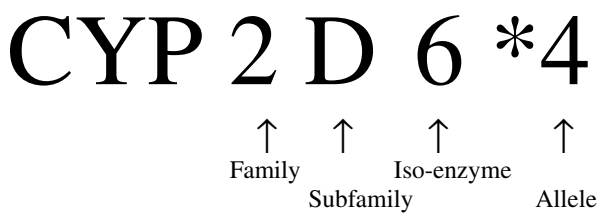

Figure 2. An example of the nomenclature of the cytochrome P450 enzymes. The number of the cytochrome P450 2D6 alleles can vary from *1 to *63. The wild type allele is indicated with *1 and has a normal functioning cytochrome P450 2D6 enzyme whereas the variant alleles of CYP2D6 indicated with the higher allele numbers have an aberrant functioning cytochrome P450 2D6 enzyme.

The metabolic capacity of the different cytochrome P450 enzymes is also defined as low affinity/high capacity or high affinity/low capacity. The CYP2D6 enzyme is, like CYP2C9 and CYP2C19, defined as a high affinity/low capacity, which implies that these cytochrome P450 enzymes prefer to metabolize specific substrates at a low concentration. As the concentration of a medicine increases, the metabolism can spill over to CYP3A4 and CYP1A2, which are low affinity/high capacity enzymes.

A difference is found between the CYP expression in the liver and the metabolic activity[20] as summarized in Table 3. In some cases probe drugs are used to investigate the metabolic activity of CYP P450.

Extra-hepatic cytochrome P450 enzymes have been identified in a wide range of tissues, which include the small intestine, pancreas, brain, lung, adrenal gland, kidney, bone marrow, mast cells, skin, ovary and testis.[21] Specific for drug metabolism, important cytochromes, such as 1A2, 2D6, 2C6 and 2C19, are discussed in detail.

Table 3. Difference between CYP P450 distribution and metabolic activity in the liver

CYP450	% Distribution	% Metabolism
3A	30	55
2C	20	10
1A2	13	2
2E1	7	1.5
2A6	4	1.5
2D6	2	30

CYTOCHROME 1A2

Cytochrome 1A2 (CYP1A2) is found exclusively in the liver and the metabolic activity is primarily hydroxylation and demethylation of compounds through oxidative metabolism. Substrates for CYP1A2 metabolism are, for example, caffeine,[22] theophylline and naproxen.[23] When any of these medicines is used with a CYP1A2 inhibitor, serum levels of the former may increase, and toxicity may result. Compounds with inhibiting capacity for CYP1A2 are, for example, grapefruit juice and drugs like fluvoxamine[24] and the fluoroquinolone antibiotic ciprofloxacin.[25] Induction of the CYP1A2 metabolism can be achieved by Brussels sprouts, broccoli, cabbage and other cruciferous vegetables, and charbroiled foods (burned meats). An important toxin that induces the working of CYP1A2 is tobacco smoke, probably through stimulation of polycyclic aromatic hydrocarbons (PAH) in the smoke.[26–28] Unfortunately CYP1A2 (along with CYP2E1, CYP1A1 and CYP1B1) often metabolizes PAHs into carcinogenic compounds.

Cytochrome 1A2 is a low affinity/high capacity enzyme in contrast to CYP2D6, CYP2C9 and CYP2C19 in the metabolism of many drugs.[29] Gender differences have been found in the Chinese population, with men having more CYP1A2 activity.[30]

CYTOCHROME 2C9

Cytochrome 2C9 (CYP2C9) is found in various tissues like the kidney, testes, glands, prostate, ovary and duodenum.[31] Most of the CYP2C9 activity in terms of drug metabolism takes place in the liver.[32] To date, 30 variant alleles of the CYP2C9 enzymes have been identified and Lee *et al.*[33] determined that two of these CYP2C9 variant alleles, *2 and *3, are found in 35% of the Caucasians. These CYP2C9 variant alleles are present much less frequently in African Americans and Asians. The genetic differences have metabolic consequences defined as EM, PM and IM (summarized in Table 4).

Some drugs such as tolbutamide[34] and phenytoin[35] have been used as probe drugs for CYP2C9 activity. Patients with the CYP2C9*2 variant allele and the CYP2C9*3 variant allele require lower maintenance doses of warfarin because of the reduced activity of these common variants. The most effective CYP2C9 inhibitors are ritonavir[36] and sulfaphenazole,[37] although the more commonly prescribed azole antifungal fluconazole[38] and the selective serotonin

Table 4. Prevalence (%) of CYP genotype in the Caucasian population

	CYP450		
Metabolizer	2D6	2C9	2C19
Extended (EM)	50	59.5	77
Intermediate (IM)	40	40	20
Poor (PM)	10	0.5	3

reuptake inhibitor fluvoxamine[38, 39] may also be categorized as strong CYP2C9 inhibitors. The only clearly recognized inducer of CYP2C9 is rifampicin. Rifampicin has been shown to reduce, by induction, serum levels of warfarin,[40] tolbutamide[41] and phenytoin.[42] An overview of cytochrome P450 enzyme substrates, inhibitors and inducers is given on a website mentioned in Table 2.

CYTOCHROME 2C19

Cytochrome 2C19 (CYP2C19) is found in many tissues, but predominantly in the liver where it accounts together with CYP2C9, for approximately 20% of the total cytochrome P450 activity. Until recently 19 different variant alleles for CYP2C9 were identified (see Table 1 for websites with information about cytochrome P450 isoenzyme variant alleles).

The prevalence of CYP2C19 enzyme polymorphisms differs between ethnic groups. For example, the PM phenotype occurs in 2–6% of Caucasians, as confirmed in our locally performed study population, and in 15–30% Asians.[43] Alam and Sharma[44] described seven different variant alleles in addition to the normal wild type. Six of the seven variant alleles are from single nucleotide changes, and the other is from an inversion of a base pair. All these variant alleles of CYP2C19 lead to reduced or no enzyme function. In general, studies have revealed that 2–6% of Caucasians (Table 4), 15–20% of Japanese and 10–20% of Africans are PMs.[45] *S*-mephenytoin has been used in the laboratory as a substrate probe for CYP2C19 activity and measuring the clearance of *S*-mephenytoin can help to establish whether a patient is a PM for CYP2C19.[46, 47] Jiang *et al.*[48] demonstrated that the area under the curve (AUC) of amitriptyline was significantly higher in PMs than in EMs, suggesting that CYP2C19 plays a role in the metabolism of amitriptyline, despite the fact that other cytochrome P450 isoenzymes (such as CYP1A2, CYP3A4 and CYP2C9) are also involved. Aoyama *et al.*[49] discovered that patients with *Helicobacter pylori* (HP) gastritis who were PMs for CYP2C19 responded better to both amelioration of symptoms and eradication HP. This outcome is thought to be due to the higher exposure to serum omeprazole in PMs. In subsequent studies, some investigators have confirmed the findings[50] while others did not support these results.[51] Determining the metabolizer phenotype may also help in the case of treatment with other drugs that rely on CYP2C19, including phenytoin, cyclophosphamide and ifosfamide. CYP2C19 inhibitors are fluvoxamine and ticlopidine, omeprazole,[52] fluoxetine[53] and ritonavir.[54] Simultaneous use of *S*-omeprazole and diazepam leads to an 81% increase in the AUC of diazepam's elimination half-life.[55] Oral contraceptives are moderate inhibitors of CYP2C19 and may cause phenytoin toxicity as phenytoin induces the metabolism of oral contraceptives. Rifampicin has been identified as an inducer of both CYP2C19 and CYP2C9.[56] Other drugs (anti-convulsants and steroids) that typically induce other cytochrome P450 enzymes may also induce CYP2C19 but to a lesser extent than they induce CYP2C9 and CYP3A4.[57]

CYTOCHROME 2D6

Although cytochrome 2D6 (CYP2D6) represents only 1–2% of the liver cytochrome P450 isoenzymes[32, 58] by weight, it is believed to be of high affinity/low capacity.[44] Although CYP2D6 plays its role in the drug metabolism mainly in the liver, CYP2D6 is also found in many other tissues, including the brain,[59] the prostate[60] and the heart.[61] CYP2D6 activity does not change with age;[62] however, CYP2D6 activity may appear to be altered because of age-associated changes in hepatic blood flow or a decrease in renal elimination of metabolites. For many drugs, especially psychotropic drugs, CYP2D6 is considered a high affinity/low capacity enzyme, which implies that CYP2D6 will preferentially metabolize drugs at lower concentrations.[32] There are ethnic differences in the distribution of EMs, PMs and UEMs. PMs are present in approximately 5–14% of Caucasians (Table 4).[63, 64] Bradford[65] indicated in a review that Asians, Pacific Islanders, Africans and African Americans have a higher percentage of reduced-function or non-functional CYP2D6 (between 40% and 50%) than do Caucasians (26%) while previous reports indicated a lower incidence of PMs in these groups.[66] UEMs carry a

duplication of a fully functional CYP2D6 allele which results in higher CYP2D6 enzyme levels. Due to these higher CYP2D6 enzyme levels, UEMs require a higher daily dose to obtain a therapeutic drug blood level. UEMs are generally rare representing 1–3% of the Caucasian population.[67] Chou *et al.*[68] studied 100 psychiatric patients in relation to their CYP2D6 genotypes and clinical outcomes. They found that PMs (12% of the study group) had more adverse medication effects and longer, more expensive hospital stays. Andreassen *et al.*[69] found that PMs were more likely to develop tardive dyskinesia over 11 years when exposed to anti-psychotics. Similarly, Ellingrod *et al.*[70] showed that heterozygotes for CYP2D6 were at higher risk of developing movement disorders when exposed to anti-psychotics compared with homozygotes for CYP2D6. Finally, Schillevoort *et al.*[71] demonstrated that PMs when treated with CYP2D6-dependent antipsychotic drugs were four times more likely to use anti-parkinsonian medications than were EMs and this was not the case among patients using non-CYP2D6-dependent anti-psychotics. An alternative method to genetic testing is to administer first a probe drug mainly metabolized by CYP2D6 and then look for specific CYP2D6 metabolites. Dextromethorphan, debrisoquin and sparteine are drugs that can be used to assess CYP2D6 activity.[72] Fluoxetine, its metabolite norfluoxetine and paroxetine are effective CYP2D6 inhibitors.[73–75] Other drugs with the potential for effective inhibition of CYP2D6 include sertraline,[76] cimetidine,[77] quinidine,[59, 78] ritonavir,[54] terbinafine[79] and ticlopidine.[80] Until now it is not elucidated whether CYP2D6 is inducible.

DISCUSSION

In the treatment of patients, doctors prescribe drugs on the basis of standardized protocols. Before registration, animal and human studies were performed to predict consistent and reproducible clinical effects of a drug. However, many clinically used drugs are effective in only 25–60% of the patients;[81] therefore it is important to determine different co-factors in the metabolism of drugs given to a specific patient as depicted in Table 1.

With the possibility of investigating genetic CYP polymorphisms more insight becomes available about the interplay of several gene products that influences the pharmacokinetics and pharmacodynamics of medications. These include the inherited differences in drug targets (e.g. receptors) and drug disposition (e.g. metabolizing enzymes and transporters), therefore polygenic determinants of drug effects have become increasingly important in pharmacogenetics.

The disadvantage of drug development is the fact that drugs are tested in a standardized population which rules out severe toxicity but will not always predict drug interaction(s). The pathways of phase I and II reactions can be clear but in many cases genetic metabolic differences, like the presence of one or multiple polymorphisms in cytochrome P450 enzymes, sometimes make it difficult to predict therapeutic drug reactions.

Although in most cases the clinical consequences may be minor, the impact can be enormous for patients receiving medicines with a narrow therapeutic index because of subtherapeutic or severe (toxic) side effects. With the population growing older, the amount of diseases or age-related afflictions is increasing and more and different medication is needed to treat patients. The elderly patient, on the other hand, is more prone to develop severe side effects, partly because of the fact that the excretory function of the kidney is lower, the liver blood perfusion is diminished and the overall metabolic function is changed.

Different patient categories could be tested for CYP polymorphisms: elderly patients with many drugs for different diseases, patients using drugs with small therapeutic range and patients with unexplained side effects. Although the genotype profile does not always predict the phenotypic expression, the interaction profile between different drugs can be estimated by a computer model available at http://www.genelex.com. Starting with a lower dose or using a medicine that is metabolized by another enzyme or route is often a way to prevent side effects and reduce interactions. Additionally, the best way to check the effect is to measure serum levels of the drug and its metabolites. However, a disadvantage is the fact that the therapeutic serum levels of many drugs are not available or expensive. In organ transplantation medicine, on the other hand, drug therapy monitoring together with cytochrome P450 genotyping is already daily practice because of the high costs and the small therapeutic range of the immunosuppressive medication.[82, 83] In this way therapeutic drug monitoring is cost effective. On the other hand, genetic polymorphisms of phase II enzymes should be developed to complete the genetic profile of the drug metabolism.

Nevertheless, genotyping should be considered to identify patients who might be at risk of severe toxic responses to environmental, pharmacological, herbal

remedies and/or nutritional stimuli, in order to guide appropriate individual dosage(s). Both clinical and genetic risk stratification (pharmacogenomics) may lead to more accurate prevention of drug-induced damage in future. Further research in a large cohort is needed to explore the clinical relevance.

An ideal situation would be the introduction of a genetic medical passport for each patient to achieve a system in which therapeutic drug monitoring will be standard clinical practice. In this way the number of side effects and related medical consumption will decrease, which in the end will lead to a better pharmacotherapy for the patients and reduced healthcare costs. To achieve this, a close cooperation between medical specialists, a hospital pharmacist, a pharmacologist and laboratory specialists will be necessary to individualize pharmacotherapy on the basis of the pharmacogenetic profile.

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