Relationship between cytochrome P450 polymorphisms and prescribed medication in elderly haemodialysis patients

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Abstract

Background: Elderly patients on haemodialysis have a high prevalence of polypharmacy and are at risk of drug-related complications. More than 80% of all prescribed drugs are metabolized by the cytochrome P450 (CYP) enzyme system. The aims of this study were to describe the prevalence of polymorphism in three CYP isoenzymes and the relationship between CYP polymorphism and prescribed drugs.

Methods: Fifty-one elderly haemodialysis patients aged ≥65 years were included. CYP-genotyping was carried out in whole blood by a real-time PCR method for detecting common variant alleles in CYP2C9, CYP2C19 and CYP2D6. The allele frequencies were calculated using the Hardy–Weinberg equation.

Results: The overall prevalence of CYP polymorphisms (heterozygous and homozygous) was 77%. The prevalence of heterozygous carriers of variant alleles coding for defective CYP2D6, CYP2C9 and CYP2C19 was 64, 22 and 55%, respectively; the prevalence of homozygous carriers was 6% for each of the CYP2D6, CYP2C9 and CYP2C19 enzymes. The prevalence of the CYP2D6*6, CYP2D6*9 and CYP2D6*41 variant alleles did not differ (p = 0.31) from that in a European Caucasian reference population. Twenty-three patients (45%) had at least one CYP mutation and used drugs that are metabolized by the CYP isoenzymes. Metoprolol and proton-pump inhibitors were the most commonly used drugs that could be affected by a heterozygous or homozygous mutation.

Conclusions: Polymorphisms of CYP2C9, CYP2C19 and CYP2D6 are common in elderly haemodialysis patients. Many of these patients have a phenotype with altered CYP enzyme activity and could benefit from close drug monitoring or a drug switch.

Keywords: Cytochrome P450, Elderly, Haemodialysis, Medication

Background

Patients with end-stage renal disease (ESRD) are treated with various medications for their kidney disease and associated comorbidities. The interindividual variability in drug response represents a clinical challenge. Factors such as age, smoking, fluid balance and other diseases influence drug effects (Samer et al. 2013). In addition, genetic variations in the cytochrome P450 (CYP) enzyme system contribute to variability in drug response through altered metabolism. More than 80% of all medications in use today are metabolized by the CYP enzyme system, which is a microsomal superfamily involved in the biosynthesis and degradation of endogenous compounds, chemicals, toxins and drugs (Trescot 2013). The most important enzymes for drug metabolism are CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

The CYP2C9 enzyme partly determines warfarin metabolism and activity, and patients with alleles CYP2C9*2 and CYP2C9*3 require lower doses to avoid bleeding (Aithal et al. 1999; Samer et al. 2013; Beyth et al. 2000; Higashi et al. 2002; Sanderson et al. 2005). Therefore, a genotype-guided dosing of warfarin has been suggested (Pirmohamed et al. 2013). The CYP2C19 enzyme metabolizes common drugs such as clopidogrel,
proton-pump inhibitors and antidepressants. The 
CYP2C19*2 and CYP2C19*3 alleles are associated with 
the clinical efficacy of clopidogrel (Umemura et al. 2008; 
Brandt et al. 2007), and hence also with the risk of cardio-
vascular events (Mega et al. 2010). The CYP2D6 enzyme 
is highly polymorphic and metabolizes various psycho-
tropic agents such as antidepressants, neuroleptics and 
opioids. The CYP2D6 poor metabolizer (PM) phenotype 
is associated with more frequent adverse drug reactions 
(Chen et al. 1996; Chou et al. 2000; Kirchheiner et al. 
2004a, b) and varying responses to analgesics such as 
codeine, tramadol and oxycodone (Samer et al. 2010a, b; 
Brousseau et al. 2007).

The prevalence of mutations in these three CYP iso-
enzymes has not previously been reported for patients 
with ESRD. However, some studies have documented 
that chronic renal failure decreases drug metabolism by lower-
ing the activity in the CYP enzyme system by circulating 
uremic toxins, increased parathyroid hormone and mark-
ers of inflammation (Dreisbach and Lertora 2008; Guevin 
et al. 2002; Michaud et al. 2005, 2006; Renton 2004).

The aims of this study involving elderly haemodialysis 
patients were to (1) describe the prevalence of CYP poly-
morphisms, (2) measure the allele frequency of each CYP 
isoenzyme and (3) determine the prescribed medication 
for patients with altered enzyme activity through CYP 
polymorphisms.

Results

The characteristics of the 51 included patients and the 
most commonly used medications are given in Table 1. 
In all 47 (92%) patients used medications metabolised by 
the CYP enzyme system; of whom 23 (45%) had geneti-
cally altered metabolism via at least one of the tested 
CYP isoenzyme.

In total, 64 and 6% of the patients were heterozygous 
and homozygous carriers of variant alleles encoding 
defective CYP2D6, respectively; these corresponding 
proportions for the alleles encoding defective CYP2C9 
were 22 and 6%, and for the alleles encoding defective 
CYP2C19 they were 55 and 6%. Of the 51 patients, 39 
(77%) had one or more CYP enzyme defects, defined as 
either heterozygous or homozygous. Furthermore, 16 
patients (31%) had two CYP defects (Table 2).

The frequencies of the CYP2C9*1, CYP2C9*2, CYP2C9*3, 
CYP2C9*1, CYP2C19*2, CYP2C19*3, CYP2C19*17, 
CYP2D6*1, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, 
CYP2D6*9, CYP2D6*10 and CYP2D6*41 alleles in the 
haemodialysis population are presented in Table 3. The 
CYP2D6 enzyme was highly polymorphic. The most 
common inactive allele was CYP2D6*4, followed by 
CYP2D6*5, CYP2D6*3 and CYP2D6*6. Although the 
CYP2D6*6, CYP2D6*9 and CYP2D6*41 alleles appeared 
to be more common in the present study population than 
among European Caucasians, the difference was not statisti-
cally significant (p = 0.31).

Most patients (47%) were identified as IM, followed by 
PM (8%). Nine single drugs and drugs belonging to two 
other drug classes were being used by IM or PM patients 
for all three CYP isoenzymes. Metoprolol was the most 
prevalent drug among the PMs and IMs of CYP2D6, 
while proton-pump inhibitors were the most frequently 
used among those for CYP2C19 (Table 4).

Discussion

To the best of our knowledge, this study is the first to 
identify the prevalence of three CYP isoenzymes 
(CYP2C9, CYP2C19 and CYP2D6) and their allele fre-
quencies in an elderly haemodialysis population, and the 
first to determine the relationship between homozygous 
and heterozygous mutations of all CYP isoenzymes and 
prescribed medications.
The main finding of this study was the high prevalence (77%) of genetic polymorphisms of three CYP isoenzymes. This finding is in line with a previous report of a high prevalence of the same three CYP isoenzymes in a high-opioid-use population (Tennant 2012) (although this was in a completely different population). However, to the best of our knowledge there is a dearth of prevalence studies for CYP polymorphisms in most common chronic diseases. This is the first study of haemodialysis patients using this approach.

The frequencies of the CYP2C9, CYP2C19 and CYP2D6 alleles have been reported elsewhere for various populations (Waade et al. 2014; Molden et al. 2002; Swen et al. 2012; Mega et al. 2011; Tamura et al. 2011). CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6 are known to be inactive alleles, and the CYP2D6*4 allele is the most common (Bradford 2002; Gaedigk et al. 1999). These four inactive alleles accounted for 29% of the CYP2D6 alleles in the present study, which is comparable with a percentage of 26% reported for a European general population (Bradford 2002). The proportion of PMs in the elderly haemodialysis population in the present study is comparable with those reported previously (Bradford 2002; McGraw and Waller 2012). However, the CYP2D6*6 and

### Table 2 Polymorphisms of the CYP enzymes CYP2C9, CYP2C19 and CYP2D6 (n = 51)

| Enzyme Enzyme activity | Genotype | Number (%) | 95 % CI, % |
|-------------------------|----------|------------|------------|
| CYP2C9 Normal           | *1/*1    | 37 (73)    | 58–84      |
| Intermediate            | *1/*2, *1/*3 | 10 (20)   | 11–35      |
| Poor                    | *2/*2, *2/*3, *3/*3 | 4 (8)     | 1–16       |
| CYP2C19 Normal          | *1/*1    | 20 (39)    | 26–54      |
| Approximately normal    | *1/*17, *2/*17 | 18 (35)   | 22–50      |
| Intermediate            | *1/*2, *1/*3 | 10 (20)   | 9–33       |
| Poor                    | *2/*2    | 2 (4)      | 0–13       |
| CYP2D6 Normal           | *1/*1    | 13 (26)    | 14–40      |
| Approximately normal    | *1/*9, *1/*41 | 10 (20)   | 10–33      |
| Intermediate            | *1/*3, *1/*4, *1/*5, *1/*6, *9/*9, *10/*10, *10/*41, *4/*41 | 24 (47) | 33–62   |
| Poor                    | *3/*4, *4/*5, *4/*5, *5/*5 | 4 (8)    | 2–19       |

95 % CI = 95 % confidence interval

### Table 3 Frequencies of CYP2C9, CYP2C19 and CYP2D6 variant alleles in the haemodialysis patients, and population reference values

| CYP enzyme and activity | Allele frequency (%) | Haemodialysis population (n = 51) | Reference populations: Caucasians a |
|-------------------------|----------------------|-----------------------------------|-------------------------------------|
| CYP2C9 Normal           | 1 a                  | 82                                | 74–91                               |
| Decreased               | 2 a                  | 8                                 | 2–14                                |
| Poor                    | 3 a                  | 10                                | 3–16                                |
| CYP2C19 Normal          | 1 a                  | 59                                | 48–69                               |
| Decreased               | 2 a                  | 21                                | 13–28                               |
| Poor                    | 3 a                  | 0                                 | 0–3                                 |
| Increased               | 17 a                 | 20                                | 12–27                               |
| CYP2D6 Normal           | 1 a                  | 54                                | 45–63                               |
| None                    | 3 a                  | 2                                 | 0–5                                 |
| 4 a                     | 21                   | 13–28                             | 11–29                               |
| 5 a                     | 4                    | 0–8                               | 1–7                                 |
| 6 a                     | 2                    | 0–5                               | 1–2                                 |
| Decreased               | 9 a                  | 4                                 | 0–9                                 |
| 10 a                    | 3                    | 0–7                               | 1–6                                 |
| 41 a                    | 11                   | 5–16                              | 8–10 b                              |

a Data from McGraw et al. (McGraw and Waller 2012)  
b Data from Preissner et al. (Sachse et al. 1997)

### Table 4 Activity of CYP enzymes and prescribed drugs potentially influenced by CYP polymorphisms (n = 51)

| CYP enzyme | Enzyme activity | Drug               | Number |
|------------|-----------------|--------------------|--------|
| CYP2C9     | Intermediate (n = 11) | Warfarin            | 1      |
|           |                  | Losartan           | 1      |
| Poor (n = 3) |                  | Warfarin           | 1      |
| CYP2C19    | Intermediate (n = 10) | Proton-pump inhibitor | 4      |
|           |                  | Diazepam           | 1      |
| Poor (n = 2) |                  | Proton-pump inhibitor | 1      |
|           |                  | Diazepam           | 1      |
| Increased (n = 1) |                  | Escitalopram      | 1      |
| CYP2D6     | Intermediate (n = 24) | Metoprolol       | 14     |
|           |                  | Codeine            | 3      |
|           |                  | Tricyclic antidepressants | 2      |
|           |                  | Tolterodine        | 1      |
|           |                  | Tramadol           | 1      |
| Poor (n = 4) |                  | Metoprolol        | 2      |
|           |                  | Bisoprolol         | 1      |
|           |                  | Tricyclic antidepressants | 1      |
CYP2D6*9 alleles were more prevalent in the present population than in Caucasian and in Central and South American Indian populations (Bradford 2002; Jorge et al. 1999; Marez et al. 1997; Griese et al. 1998; Gaedigk et al. 1999; Sachse et al. 1997). The previously reported frequencies of the CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles are similar to those reported here (Rudberg et al. 2008; Sim et al. 2006; Kurzawski et al. 2006).

A study involving non-institutionalized patients aged >60 years found that medications metabolized by CYP systems were used by 62 % of patients (Cabrera et al. 2009), versus 92 % in the present study. Elderly patients are known to be exposed to higher drug concentrations for a given dose compared to younger adults (Waade et al. 2012), due to multiple factors such as reductions in hepatic blood flow, cardiac output and renal function. Both renal failure and genetically reduced or absent enzyme activity increase the vulnerability to side effects. A recent report confirmed the effects of age on exposure to antidepressants in patients with the CYP2C19 and CYP2D6 PM genotypes (Waade et al. 2014). This study was subject to some limitations. First, there was no comparator healthy control group of elderly subjects, which would have enabled a better understanding of the genetic variation of the three CYP isoenzymes and their allele frequencies. Second, as no measurements of drug levels were performed to investigate the effect of altered CYP isoenzymes on the elimination of the drugs, the study was unable to show the practical impact of these polymorphisms in this population. Finally, most of the study patients were European Caucasians, hence limiting the generalizability of the findings.

In general, the use of pharmacogenetic testing in clinical settings has the potential to improve patient outcomes and the long-term cost of care through reduction of polypharmacy and risk of drug-related problems (Dorfman et al. 2013), although the practical implications of detected CYP enzyme polymorphism are not yet clear. Some studies including CYP genotyping have provided useful information about medication dosages, or have led to changes in treatments (Pirmohamed 2014; Molden et al. 2002; Mega et al. 2011; Pettersen et al. 2011). The US Food and Drug Administration has published a list of nearly 100 drugs with a recommendation for genetic testing (FDA 2014). Similarly, the Dutch Pharmacogenetics Working Group guidelines recommend dose adjustments in 5–10 % of drugs prescribed to patients with altered CYP2D6 and CYP2C19 metabolism, and increased awareness for an adverse drug response in all these patients (Swen et al. 2012). Thus, the finding of a CYP enzyme abnormality does not necessarily require dose adjustment.

Conclusions
In conclusion, a high prevalence of three CYP isoenzymes was found in elderly haemodialysis patients at the level of the general population. About 45 % of these patients had one or more mutations in their CYP isoenzymes and used medications for which the metabolism may be affected by such mutations. These patients may benefit from close drug monitoring or a drug switch. The actual impact of these mutations on drug serum levels is a topic for future studies.

Methods
Study population and data collection
This study was performed between July and December 2012 in the dialysis centre at Akershus University Hospital, Norway. This hospital has a catchment area comprising about 480,000 inhabitants. Of the 102 haemodialysis patients screened at the start of the study, 52 were ≥65 years of age and eligible for inclusion. One patient died before assessment; the remaining 51 patients participated in the study.

The following patient data were collected via review of their medical records: medical history, comorbidities (evaluated using the Charlson comorbidity index), dialysis treatment quality index (quantified in units of Kt/V), haemodialysis access and medication history. Blood samples were drawn at the start of dialysis treatment on the day of a regularly scheduled haemodialysis session.

Our institute ethical committee evaluated the study protocol and approved the study. All participants gave their consent at the start of the study.

Genotyping of CYP enzymes
Venous blood samples (with EDTA as anticoagulant) were genotyped at the Centre for Psychopharmacology, Diakonhjemmet Hospital, Norway. A real-time PCR method was applied using mutation-specific TaqMan probes (Life Technologies, Foster City, CA, USA) (Schaeffeler et al. 2003). Genomic DNA was extracted instrumentally from leukocytes prior to applying the PCR using a MagNA Pure LC DNA Isolation Kit I (Roche Diagnostics, Oslo, Norway). The genotyping assay included detection of the single-nucleotide polymorphisms specific for the following variant alleles: CYP2C9*2 and CYP2C9*3; CYP2C19*2, CYP2C19*3, CYP2C19*4 and CYP2C19*17; and CYP2D6*3, CYP2D6*4, CYP2D6*6, CYP2D6*9, CYP2D6*10 and CYP2D6*41. In addition, copy-number analyses was implemented to establish the presence of CYP2D6 gene deletion (CYP2D6*5) or multiplication. The absence of
mutated alleles was interpreted as the presence of the functional wild-type allele (CYP2D6*1). The genotyping assay did not discriminate between functional and non-functional CYP2D6 multiplications.

Classification of enzyme activity

A genotype-predicted phenotype was assigned to each patient. For CYP2D6, intermediate metabolizers (IMs) were defined as patients carrying two reduced-activity alleles (CYP2D6*9, CYP2D6*10 and CYP2D6*41) or carrying one inactive allele (CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6). Poor metabolizers (PMs) were defined as patients carrying two inactive alleles (CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6). For CYP2C19 and CYP2C9, IMs were defined as patients with one inactive allele (CYP2C19*2, CYP2C19*3, CYP2C9*2, and CYP2C9*3), while PMs were defined as patients carrying two inactive alleles.

Statistical analyses

Descriptive statistics are presented as median (range or 25th–75th percentiles) or number (%) values as appropriate. The allele frequencies were calculated using the Hardy–Weinberg equation and compared to published general population references for European Caucasians (McGraw and Waller 2012). Groups were compared using Fisher’s exact test. All analyses were carried out using SPSS statistical software (version 19, IBM, SPSS, Chicago, IL, USA). The threshold for statistical significance was set at $p < 0.05$ (two-sided tests). The study was approved by the privacy ombudsman of Akershus University Hospital.

Abbreviations

CYP: cytochrome P 450; DNA: deoxyribonucleic acid; ESRD: end stage renal disease; IM: intermediate metabolizer; PCR: polymerase chain reaction; PM: poor metabolizer.

Authors’ contributions

KP Idea generator, design of the study, collecting data and writing the manuscript. TH, WA and KS manuscript draft, manuscript design and manuscript review. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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