

Cytochrome P4503A pharmacogenetics

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Because of its abundance in the intestine and liver, CYP3A, a term that in adults reflects the collective activity of CYP3A4, CYP3A5, and CYP3A7, plays a central role in the metabolism of a wide variety of therapeutic compounds and is responsible for the metabolism of more than 50 % of drugs in the market [1] (see Table for a list of drugs used in anti-HIV pharmacotherapy metabolized by CYP3A). There is a large overlap in the specificity of these isozymes towards their substrates [2-4]. This is clinically important because it potentially reduces the influence of genetic heterogeneity of *CYP3A* genes on the pharmacokinetics of CYP3A dependent drugs. This assumption is supported by the broad unimodal curve, with no evidence of the existence of poor or ultra rapid metabolizers, when phenotyping subjects without comedications and/or diet affecting CYP3A activity with classical CYP3A substrates such as the benzodiazepine midazolam [5-8], the anti-hypertensive nifedipine [9] or the antibiotic erythromycin [5]. This assumption is also reflected by the modest interindividual variability (usually 3 - 4 fold) of the metabolic clearance of CYP3A phenotyping probes [5-8,10,11], a deficiency of one CYP3A isozyme (in particular of CYP3A5 and/or CYP3A7) being partially compensated by the activity of other isozyme (in particular CYP3A4). However, rare cases of CYP3A poor metabolizers, with the simultaneous occurrence of mutations in different isoforms, leading to very low or null CYP3A activity, have been described (see below).

On the other hand recent studies have shown, for some drugs, clinically significant differences in the catalytic activity of CYP3A isoforms [12,13]. For example, using recombinant CYP3As, a higher or lower intrinsic clearance mediated by CYP3A5 have been shown for the immunosuppressants tacrolimus and sirolimus, respectively, as compared to CYP3A4 [12,13]. This result is in agreement with the 3-fold higher tacrolimus clearance [14], and the 3 to 6 fold lower dose-adjusted tacrolimus trough plasma concentrations [15] measured in CYP3A5 extensive metabolizers (*1/*1 and *1/*3) as compared to poor metabolizers (*3/*3). A higher intrinsic clearance mediated by CYP3A4 as compared to CYP3A5 has also been measured for the antihypertensive verapamil [16].

There is a similar overlap in the specificity of CYP3A isoforms towards inhibitors, although

differences in the sensitivity have been described. The immunosuppressant cyclosporine and the antifungals ketoconazole and fluconazole have for example been shown to be more potent inhibitors of CYP3A4 than CYP3A5 [12,17]. Similarly, although the protease inhibitors amprenavir, indinavir, nelfinavir, ritonavir and saquinavir inhibit all CYP3A isoforms, some differences in their inhibitory potential could also be demonstrated, depending on the CYP3A isoforms [18] (see table for inhibition of CYP3A isoforms by drugs used in anti-HIV pharmacotherapy). Because of the marked decrease of metabolic clearance observed for CYP3A substrates when inhibitors such as ritonavir, nelfinavir [19] or ketoconazole [7] are administered, leading to simultaneous inhibition of CYP3A isoforms, and because such drug combinations are not rare, metabolic interactions with CYP3A inhibitors are of high clinical relevance.

CYP3A4

CYP3A4, along with the three other CYP3A genes (CYP3A5, CYP3A7, CYP3A43), is located on chromosome 7q22.1 [20]. CYP3A4 is the major form of human P450, both for the amount of protein expressed (about 25 % of all hepatic P450) and the importance in drug metabolism. CYP3A4 is also extensively expressed in the intestine (50 % of hepatic content and 70 % of total P450 present) [11]. The extent of interindividual variability of CYP3A4 activity is presently difficult to determine. Conflicting results have been published on the expression of CYP3 isoforms when using isozyme specific antibodies, possibly due in part to the cross-reactivity of antibodies, even when monoclonal antibodies were used [21]. The hepatic expression of CYP3A4 mRNA exhibits a unimodal distribution [22], indicating the involvement of multiple genetic and/or environmental factors into this trait [21]. *CYP3A4* gene expression varied by a factor of 118 in 63 liver samples obtained by surgery from individuals of white European origin but drug exposure in some of these subjects prior to surgery may have contributed to the observed high interindividual variability [22]. Much lower interindividual variability is observed in vivo with CYP3A phenotyping probes [5-8,10] but none of the used phenotyping drugs were specific for CYP3A4. Interestingly, a high intestinal mRNA expression of

CYP3A4 has been shown to be associated with a poor survival rate during the first post-operative year in living-donor liver transplant patients treated with tacrolimus [23].

To date (<http://www.cypalleles.ki.se/cyp3a4.htm>; accession date 13.8.07) 39 allelic variants of the *CYP3A4* gene have been described. However, functional characterisations of most CYP3A4 variants reveal a limited impact on protein expression or activity [21] and, until very recently, only two variants (*CYP3A4*1B* and *CYP3A4*20*) have been shown to alter CYP3A4 function in vivo. Conflicting results were published on the functional consequences of the *CYP3A4*1B* allele, which corresponds to a polymorphism in the 5'-promoter region [24-27], with a frequency of 4 % and 67 % in Caucasians and black subjects, respectively [28,29]. Linkage disequilibrium of *CYP3A4*1B* allele and the *CYP3A5*3* allele might also contribute to the discrepant results [6]. A subject with a low systemic midazolam clearance was identified as heterozygous carrying a novel *CYP3A4* allele (named *CYP3A4*20*) with a premature stop codon yielding a truncated protein which does not incorporate heme and is thus devoid of catalytic activity. The subject was also found to be a CYP3A5 poor metabolizer (homozygous for the *CYP3A5*3* allele). Genotyping of a white German population (n=428) revealed that *CYP3A4*20* is a rare allele (<0.06 %). However, the most interesting result on genetic markers of CYP3A4 expression was reported recently, with associations between the hepatic CYP3A4 protein expression levels and enzymatic activity and genetic polymorphisms from two regions within the *CYP3A* gene cluster, one defined by several variants mostly located within *CYP3A7*, the other by a single nucleotide polymorphism in intron 7 of *CYP3A4* (rs4646437C>T) [30]. Interestingly, the effects of these SNPs may be sex-dependent, with the same variant having opposite effects in men and women [30]

CYP3A genes are under the transcriptional control of nuclear receptors such as the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), and the hepatocyte nuclear factor-4alpha (HNF4alpha) [29,31,32]. In adult livers, HNF4alpha and/or CAR regulates the constitutive CYP3A expression, whereas PXR mediates the induction by exogenous compounds [29]. Genetic polymorphisms of nuclear receptors could therefore influence *CYP3A* gene expression [29,32,33] and CYP3A activity, which has been confirmed in a few studies [34-36]. Because of the simultaneous effect of nuclear receptors on *CYP3A* genes, marked increases of CYP3A activity are observed following the exposure to CYP3A inducers (i.e. drugs or xenobiotics) [7],

which illustrates the influence of environment on CYP3A activity (see Table for CYP3A induction by drugs used in anti-HIV pharmacotherapy).

CYP3A5

CYP3A5 is expressed at a much lower level in the liver as compared to *CYP3A4*, but it has a wider tissue distribution. To date (<http://www.cypalleles.ki.se/cyp3a4.htm>; accession date 13.8.07) 23 allelic variants of the *CYP3A5* gene have been described, the most common *CYP3A5*3* allele being present at frequencies between 27% in African-Americans and 95% in Caucasians. *CYP3A5*3* creates a cryptic consensus splice site that results in the production of a small quantity of properly spliced mRNA, with only subjects with at least one *CYP3A5*1* allele expressing large amounts of CYP3A5 [20,37]. Since CYP3A5 can represent up to 50 % of the total hepatic CYP3A content in *CYP3A5*1/*1* subjects, it has been suggested that polymorphically expressed *CYP3A5* may be an important genetic contributor to interindividual differences in CYP3A dependent drug clearance [20]. This was not confirmed in studies showing no or small differences between CYP3A5 poor or extensive metabolizers in the oral clearance of CYP3A drugs such as midazolam [8,10,38,39], the opioid drug methadone [27], or the cytotoxic agent docetaxel [10]. This could be explained by a compensatory activity of CYP3A4 in CYP3A5 poor metabolizers, or to a stronger catalytic activity of CYP3A4 towards these drugs, as compared to CYP3A5.

The difference of oral clearance remains weak for drugs such as the protease inhibitor indinavir, the calcium channel blocker amlodipine or the benzodiazepine alprazolam, with up to 50 % higher clearance measured in CYP3A5 expressors [40-42]. On the other hand, stronger differences were found between CYP3A5 poor and extensive metabolizers (about 2 fold difference) for tacrolimus, sirolimus (despite an in vitro higher intrinsic clearance of sirolimus mediated by CYP3A4 than CYP3A5 [12]) or saquinavir [14,43-45]. However, possibly in part due to a mandatory therapeutic drug monitoring of immunosuppressants, with subsequent dose adaptation according to the plasma levels, no clinical consequences of *CYP3A5* genetic polymorphism could be demonstrated for tacrolimus or sirolimus [14,43]. Based on the results showing an influence of *CYP3A5* genotype on the therapeutic response to statins (stronger reduction in serum cholesterol with lovastatin, simvastatin and atorvastatin in poor metabolizers [46]) and side-effects (increased muscle damage with increased creatinine kinase following myalgia with artovastatin in poor metabolizers [47]), studies should be performed in the future to extend

our knowledge on the clinical consequence of *CYP3A5* genetic polymorphism.

Of interest is the recently demonstrated possible physiological role of *CYP3A5*: this isozyme being the lone *CYP3A* enzyme expressed in the kidney and metabolizing cortisol to its 6 β -hydroxy metabolite, its activity could therefore influence renal tubular sodium reabsorption [48,49]. Although discrepant results have been published [50-53], recent studies suggest that when variables such as age and sodium intake are taken into account, *CYP3A5* genetic polymorphisms are associated with ambulatory blood pressure [48,49]

CYP3A7

Like *CYP3A5*, *CYP3A7* activity is distributed bimodally, indicating the existence of a polymorphism [29]. *CYP3A7* was originally thought to be exclusively fetal, but recent studies have demonstrated its expression in 11-88% of adult livers, with approximately 20% of them showing high levels of expression, with *CYP3A7* contribution up to 20% of the total *CYP3A* [54]. To date (<http://www.cypalleles.ki.se/cyp3a4.htm>; accession date 13.8.07) 6 allelic variants of the *CYP3A7* gene have been described. Of particular interest is the *CYP3A7*1C* which was shown to be a marker of *CYP3A7* expression in liver and intestine [55,56], and to be present at an allelic frequency of 3% in Caucasians and 6% in African-Americans [20]. Clinical studies on the influence on *CYP3A7* on drug pharmacokinetics are presently lacking but should be the subject of future investigations.

CYP3A43

This novel isozyme has been identified as a result of the human genome project [11]. However, because of a low mRNA expression (about 0.3 % of that of *CYP3A4* in human livers) [22] and because of a low *CYP3A* activity when expressed in bacteria and when measuring the metabolism of testosterone, a *CYP3A* substrate, this isozyme most probably plays no significant role in drug metabolism in humans [11].

FINAL REMARKS

It is expected that, in the near future, several studies will be published exploring the influence of the rs4646437C>T SNP located in intron 7 of *CYP3A4* gene (or of other unknown nearby variant in strong linkage disequilibrium) [30], and of the *CYP3A5* and *CYP3A7* genetic polymorphisms on the kinetics of drugs metabolized by *CYP3A*. Such studies, with others examining differences in the catalytic activity of *CYP3A* isoforms will considerably increase our understanding of the pharmacokinetics and

pharmacodynamics, and therefore the safety and efficacy of a very large number of drugs.

Metabolism of anti-HIV drugs by *CYP3A* isoforms [18,45,57-62]

Drug	Metabolism (a)(b)	Inhibitor (b)	Inducer (b)	
NNRTIs	Nevirapine	3A4 <i>2B6</i>	minimal inhibition: 3A4, 2D6, 1A2	3A4, 3A5, 2B6
	Efavirenz	2B6 <i>3A4, 3A5, 2A6</i>	potent inhibition: 3A4, 2C9, 2C19 weak inhibition: 2D6, 1A2	3A4, 3A5, 2B6
	Delavirdine	3A4 <i>2D6</i>	potent inhibition: 3A4, 2C9, 2C19 minimal inhibition: 2D6, 1A2	
PIs	Saquinavir	3A4, 3A5	potent inhibition: 3A4, 3A5 moderate inhibition: 3A7	potent induction: 3A4 moderate induction: 1A2, 2C9, 2C19
	Ritonavir	3A4, 3A5 <i>2D6</i>	potent inhibition: 3A4, 3A5, 3A7 (3A7 less potent than 3A4 and 3A5) moderate inhibition: 2D6, 2C9, 2C19, 2B6	
	Indinavir	3A4, 3A5	potent inhibition: 3A4 moderate inhibition: 3A5 weak inhibition: 3A7	
	Nelfinavir	3A4 <i>2C19, 2D6</i>	potent inhibition: 3A4, 3A5, 3A7 moderate inhibition: 1A2, 2B6	2C9 (possibly)
	Amprenavir	3A4, 3A5	potent inhibition: 3A4, 3A5 (3A5 less potent than 3A4) moderate inhibition: 3A7	3A4
	Lopinavir	3A4	3A4, 2D6	3A4
	Atazanavir	3A4	potent inhibition: 3A4 1A2, 2C9	

a) major pathway in bold, minor pathway in italics

b) not all studies examined each *CYP3A* isoforms separately and an absence of indication on *CYP3A5* and/or *CYP3A7* does not exclude their involvement in the metabolism of, the inhibition by and/or the induction of the compound of interest

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