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Relevance of UDP-glucuronosyltransferase polymorphisms for drug dosing: A quantitative systematic review

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ABSTRACT

UDP-glucuronosyltransferases (UGT) catalyze the biotransformation of many endobiotics and xenobiotics, and are coded by polymorphic genes. However, knowledge about the effects of these polymorphisms is rarely used for the individualization of drug therapy. Here, we present a quantitative systematic review of clinical studies on the impact of *UGT* variants on drug metabolism to clarify the potential for genotype-adjusted therapy recommendations.

Data on UGT polymorphisms and dose-related pharmacokinetic parameters in man were retrieved by a systematic search in public databases. Mean estimates of pharmacokinetic parameters were extracted for each group of carriers of UGT variants to assess their effect size. Pooled estimates and relative confidence bounds were computed with a random-effects meta-analytic approach whenever multiple studies on the same variant, ethnic group, and substrate were available.

Information was retrieved on 30 polymorphic metabolic pathways involving 10 UGT enzymes. For irinotecan and mycophenolic acid a wealth of data was available for assessing the impact of genetic polymorphisms on pharmacokinetics under different dosages, between ethnicities, under comedication, and under toxicity. Evidence for effects of potential clinical relevance exists for 19 drugs, but the data are not sufficient to assess effect size with the precision required to issue dose recommendations.

In conclusion, compared to other drug metabolizing enzymes much less systematic research has been conducted on the polymorphisms of UGT enzymes. However, there is evidence of the existence of large monogenetic functional polymorphisms affecting pharmacokinetics and suggesting a potential use of UGT polymorphisms for the individualization of drug therapy.

Contents

Abbreviations: A, Adenine; Afr, Africans; As, Asians; AUC, area under the curve; C, Cytosine; Cauc./Cau, Caucasians; Cl, Clearance; Cl_{Het}, Clearance of the heterozygous alleles; Cl_{Hom}, Clearance of the homozygous alleles; Cl_{Wt}, Clearance of the wild-type alleles; C_t, trough concentration; cyc, Cyclosporine; E_{Het}, genotype effects of the heterozygous alleles; E_{Hom}, genotype effects of the homozygous alleles; E_{Wt}, genotype effects of the wild-type alleles; G, Guanine; Het, Heterozygous; HIV, human immunodeficiency virus infection; Hom, Homozygous; i.e., id est (that is); MD, multiple dose; NSAID(s), non-steroidal antiinflammatory drugs; PharmGKB, Pharmacogenomics Knowledgebase; PK, pharmacokinetics; ref./Ref, Reference; SD, single dose; Sign, Significant; sir, Sirolimus; SN-38, metabolite of Irinotecan; T, Thymine; tac, Tacrolimus; UDP, uridine diphosphate; UGT, UDP-glucuronosyltransferase; Wt, wild type.

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1. Introduction

1.1. Genetics and classification

UDP-glucuronosyltransferase (UGT) enzymes catalyze the conjugation of many drugs and environmental compounds (Meech et al., 2012). UGTs also play vital roles in the conjugation of endobiotics including steroids and thyroid hormones, fatty acids, bile acids and bilirubin (Guillemette, 2003). While in most cases inactivated, substrates may in some instances be bioactivated by glucuronidation, as shown by the case of morphine 6-glucuronide (Portenoy et al., 1992; Ulens et al., 2001). In other cases, activation by glucuronidation may lead to toxic compounds. The glucuronidation of carboxylic remnants in particular may give origin to reactive acylglucuronides (Bailey & Dickinson, 2003), like the acylglucuronides of bilirubin, retinoic acid, several NSAIDs, and mycophenolic acid (MMF) (Wieland et al., 2000). Some of these reactive acylglucuronides may cause cytotoxicity or immunotoxicity.

UGT enzymes are classified into different families (number), subfamilies (letter) and genes (number). The 22 human UGTs are classified into five subfamilies: 1A, 2A, 2B, 3A, and 8. The 1A subfamily includes UGT1A1 and UGT1A3-10, while UGT1A2p, 11p, 12p and 13p are nonfunctional pseudogenes (Desai et al., 2003). All UGT1A enzymes are coded by a single gene locus on chromosome 2 differing in the first exon while sharing exons 2 to 5 (Mackenzie et al., 2005). As a consequence, genetic polymorphisms in the shared exons 2 to 5 affect all enzymes of this family at the same time. In addition, there is pronounced linkage between the exons 1 and the shared exons 2 to 5 (Menard et al., 2009; Riedmaier et al., 2010).

The UGT enzymes 2A1 and 2A2 are similarly coded by a single gene locus on chromosome 4q13 differing in the first exon and sharing exons 2–6. The UGT2B subfamily genes are also located on chromosome 4 and are coded by six non-shared exons (Guillemette et al., 2010).

In Caucasians, complete deletions of UGT2B17 and 2B28 were found with minor allele frequencies of 27.5% and 13.3%, respectively (Menard et al., 2009).

UGT enzymes are mainly expressed in the liver and the intestine. In particular, UGT1A, -1A8 and -1A10 are expressed almost exclusively in the gastrointestinal tract. Therefore, polymorphisms in these enzymes should result in more pronounced pharmacokinetic differences after oral compared with systemic administration. However, these differences may be obliterated by enterohepatic recirculation. A few UGTs are expressed in other organs such as the kidneys (1A5, 1A6, 1A7, 1A9, 2B4, 2B7 and 2B17) and some in endocrine glands (Nakamura et al., 2008; Court et al., 2012; Knights et al., 2013). UGT1A4, 1A6 and 2B7 are expressed in the brain (King et al., 1999; Brands et al., 2000). The picture of the tissue expression of different UGTs may change in the future as data from quantitative protein mass spectrometry become increasingly available.

UGT enzymes are genetically polymorphic. More than 200 alleles have been described for the *UGT1* and *UGT2* gene families influencing enzymatic function, cellular trafficking or gene expression, thereby possibly modulating individual drug exposure (http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/). Many more variants have been identified with no or as yet unknown functional role.

1.2. Role of uridine diphosphate-glucuronosyltransferases enzymes in drug metabolism

In drug metabolism, glucuronidation leads to more hydrophilic metabolites that are subsequently excreted via the kidneys or the bile and the gut depending on their residual hydrophobicity and affinity to transport proteins. In both cases, genetic polymorphisms causing low glucuronidation activity will lead to lower drug clearance. Consequently, lower dosages may be indicated to compensate the effects of the genetic polymorphism. In contrast, when glucuronidation leads to bioactivation and/or possibly toxic compounds, drug switching is a more appropriate response than dose adjustment.

Biliary excreted glucuronides may undergo enterohepatic recirculation. Once reabsorbed, they may contribute to the total bioavailability of the parent drug, as in the example of MPA glucuronidation (Levesque et al., 2008). By affecting enterohepatic recirculation, genetic variation in glucuronidation may have a different impact on the parent drug pharmacokinetics than one might expect from in vitro glucuronidation assays.

Drug glucuronidation appears to be almost exclusively catalyzed by members of the UGT1 and UGT2 families (Meech et al., 2012). As shown in Fig. 1, which is compiled from the number of drugs where UGT enzymes are involved according to Table 2, the UGT enzymes 1A1, 1A3, 1A4, 1A9 and 2B7 together metabolize the majority of substrates. These UGTs may therefore play an important role in the metabolism of many commonly used drugs, implying that variation in the genes coding for these enzymes may be particularly relevant. Other UGTs such as UGT2B15 appear to display more specific affinities, but were much less studied concerning their impact in drug metabolism.

Within the UGT1 family, UGT1A1, -1A3, -1A4, and -1A6 to -1A10 are involved while UGT1A5 does not appear to play a role in drug metabolism (Finel et al., 2005). At present there are no data indicating a role in drug metabolism for the UGT2A group (Court et al., 2008; Meech et al., 2012).

UGT2B7, -2B15, and -2B17 are important in liver drug metabolism (Guillemette et al., 2010) (Fig. 1). UGT2B17 and 2B28 are among the most commonly deleted genes in humans. At present, the available findings give no indication that UGT2B28 plays a role in drug metabolism (Ohno & Nakajin, 2011). However, these null results should be viewed with caution, since most UGT enzyme screenings have been conducted without including all these genes systematically in the panel.

The most extensively studied genetic polymorphism in UGT enzymes is the polymorphic gene locus *UGT1A1*. Complete or almost complete deficiency of *UGT1A1* results in the rare Crigler Najjar Syndrome type I and type II, respectively (Crigler & Najjar, 1952). Quite frequent is the benign inherited unconjugated hyperbilirubinemia (Gilbert's syndrome) (Bosma et al., 1995). Among Caucasians, the most frequently underlying genetic variation is characterized by 7 instead of 6 TA repeats in the promoter (*UGT1A1*28*) leading to a decrease in gene transcription (Beutler et al., 1998). Among Asians, *UGT1A1*6* and some other variants are contributing to Gilbert's syndrome. Individuals with Gilbert's syndrome exhibit lower glucuronidation rates when medicated with several HIV drugs and irinotecan (Carulli et al., 1976; Prueksaritanont et al., 2002a; Lankisch et al., 2006, 2008). Beyond these effects of the UGT1A1 polymorphisms on glucuronidation of UGT1A1 drug substrates, there are already several examples for a metabolic crosstalk or gene–environment interaction: carriers of the *UGT1A1*6* and **28* variants are apparently much more likely to develop jaundice after medication with methotrexate, indinavir,

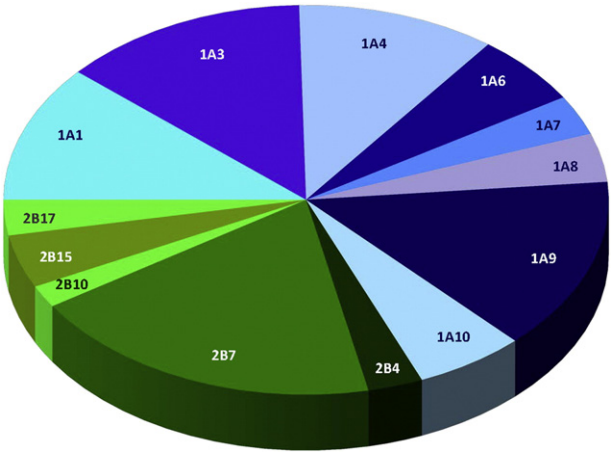

Fig. 1. Pie chart representing the relative importance of individual UGT enzymes in drug metabolism as the proportion of drugs that are known substrates of each UGT enzyme, based on data summarized in Table 2.