Available online at www.sciencedirect.com

SCIENCE DIRECT®

Pharmacology & Therapeutics 106 (2005) 97–132

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

UDP-glucuronosyltransferases and clinical drug-drug interactions

Tony K.L. Kiang[a], Mary H.H. Ensom[a,b], Thomas K.H. Chang[a,*]

[a]*Faculty of Pharmaceutical Sciences, The University of British Columbia, 2146 East Mall, Vancouver, British Columbia, V6T 1Z3, Canada*
[b]*Department of Pharmacy, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia, V6H 3N1, Canada*

Abstract

UDP-glucuronosyltransferase (UGT) enzymes catalyze the conjugation of various endogenous substances (e.g., bilirubin) and exogenous compounds (e.g., drugs). The human UGT superfamily is comprised of 2 families (UGT1 and UGT2) and 3 subfamilies (UGT1A, UGT2A, and UGT2B). Many of the individual UGT enzymes are expressed not only in liver but also in extrahepatic tissues, where the extent of glucuronidation can be substantial. Several others (e.g., UGT1A7, UGT1A8, and UGT1A10) are expressed only in extrahepatic tissues. The molecular regulation of UGT enzyme is still not fully understood, but various transcription factors appear to play a regulatory role. The expression of individual UGT enzymes is subject to genetic polymorphism and these enzymes can be inhibited or induced by xenobiotics. Experimental evidence in humans indicates that the glucuronidation of acetaminophen, codeine, zidovudine, carbamazepine, lorazepam, and propafenone can influenced by specific interacting drugs. In contrast, the glucuronidation of diflunisal, morphine, naproxen, and temazepam is not affected appreciably by the drugs investigated to date. In general, UGT-mediated human drug interaction studies are difficult to interpret. The factors that complicate the interpretation of this type of drug interaction data are discussed.

Keywords: UDP-glucuronosyltransferase; UGT1A; UGT2A; UGT2B; Glucuronidation; Drug interaction

Abbreviations: $Ae_{t\text{-}ss}$, the amount of total drug excreted in urine during one dosage interval; AUCi, area under the plasma concentration-time curve in the presence of an inhibitor; AUC, area under the plasma concentration-time curve; AZT, zidovudine; C-6-G, codeine-6-*O*-glucuronide; CL/F, oral clearance; $CL_{f(o)AMT}$, formation clearance of 3′-amino-3′-deoxythymidine; $CL_{f(o)GZDV}$, formation clearance of zidovudine glucuronide; CL, clearance; CL_R, renal clearance; C_{max}, maximum serum concentration; C_{max}^{ss}, maximum serum concentration achieved at steady state; C_{min}, minimum serum concentration; C_{min}^{ss}, minimum serum concentration achieved at steady state; CsA, cyclosporine A; F, bioavailability; G-AZT (GZDV), zidovudine glucuronide; HIV, human immunodeficiency virus; K_a, terminal elimination rate constant; K_i, inhibition constant; K_m, concentration of substrate that gives half of the maximal enzyme activity; M/P ratio, the metabolite to parent compound ratio; M-3-G, morphine-3-*O*-glucuronide; M-6-G, morphine-6-*O*-glucuronide; MMF, mycophenolate mofetil; MPAG, mycophenolic acid glucuronide; MRT, mean residence time; $t_{1/2}$, elimination half-life; TCAs, tricyclic antidepressants; T_{max}, time required to reach maximum serum concentration; UGT, UDP-glucuronosyltransferase; V_d, volume of distribution; V_{max}, maximum enzyme activity; $\sum X_{GZDV}$, cumulative mg equivalents of AZT glucuronide eliminated in urine as unchanged drug; $\sum X_{ZDV}$, cumulative mg equivalents of AZT eliminated in urine as unchanged drug.

Contents

* Corresponding author. Tel.: 604 822 7795; fax: 604 822 3035.
E-mail address: tchang@interchange.ubc.ca (T.K.H. Chang).

0163-7258/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2004.10.013

1. Introduction

Biotransformation is one of the important processes that determine the pharmacokinetic profile of an administered drug. For a drug that undergoes biotransformation, several factors, such as the patient's physiological status, genetic make-up, and coadministered medications, may influence the extent of biotransformation and lead to toxic or subtherapeutic drug concentrations. The area of drug-drug interaction has received notable attention as a result of increased understanding, at the molecular level, of the enzymes responsible for drug biotransformation. In particular, studies have focused on cytochromes *P*450 and the potential for drug interactions mediated by these enzymes. As a result of the abundant research conducted on this superfamily of enzymes, many reviews on cytochrome *P*450-mediated drug interactions have been published (e.g., Michalets, 1998; Tanaka, 1998; Dresser et al., 2000). In contrast, other drug-metabolizing enzymes, such as the phase II conjugating enzymes, have received less attention. However, conjugating enzymes are important because many drugs and their metabolites undergo conjugation reactions (Miners et al., 2004). Among the phase II enzymes are the UDP-glucuronosyltransferases (UGTs), which recognize a multitude of functional groups and utilize a common co-substrate, UDP-glucuronic acid, in their conjugating reactions. In fact, UGT-catalyzed glucuronidation reactions are responsible for ~35% of all drugs metabolized by phase II enzymes (Evans & Relling, 1999). Therefore, it is important to enhance our understanding of the function and regulation of UGT enzymes and the role they play in metabolic drug interactions. The purpose of this review article is to systemically evaluate the scientific literature on inhibition and induction of drug glucuronidation in humans. Only those studies that quantified glucuronide levels will be reviewed. A brief overview on the function, tissue distribution, molecular regulation, pharmacogenetics, inhibition, and induction of UGT enzymes is also provided.

2. Human UDP-glucuronosyltransferase enzymes

The human UGTs are a superfamily of enzymes that conjugate a variety of endogenous substances and exogenous compounds. Examples of endogenous substrates for UGT include bilirubin, steroid hormones, thyroid hormones, bile acids, and fat-soluble vitamins. Examples of exogenous substrates for UGT include drugs, chemical carcinogens, environmental pollutants, and dietary substances (Ritter, 2000; Tukey & Strassburg, 2000). UGT enzymes are bound to the internal membrane and face the luminal side of the endoplasmic reticulum, a location which confers both an advantage and a disadvantage (Tukey & Strassburg, 2000). The advantage is that these enzymes have direct access to metabolites produced by phase I biotransformation reactions. The disadvantage is that this restricts the access of drug substrates, cofactors, and glucuronidated products to and from the active sites of UGT enzymes. This access restriction by the endoplasmic reticulum is one of the factors that causes a recognized decrease in UGT enzyme activity in isolated microsomes and is the phenomenon commonly referred to as "latency." This contributes to one of the difficulties in predicting in vivo effects of UGT enzymes based on data obtained from in vitro experiments, such as those with tissue microsomes (Fisher et al., 2001; Lin & Wong, 2002). Finally, there appears to be sex (Court et al., 2001; Meibohm et al., 2002) and developmental differences (de Wildt et al., 1999; McCarver & Hines, 2002) in the expression of specific UGT enzymes.