Behind CYP450 interaction tables – the effect of gender and age on pharmacokinetics

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17th Congress
21-23 March
2012 Milan, Italy

PHC006

BACKGROUND AND OBJECTIVES

If not incorporated as physiological substrates, drugs and food components are identified as **xenobiotics**. The risk of interactions increases with the number of substrates administrated. Interaction tables are restricted to unspecific isoenzymes of the families CYP1, CYP2, and CYP3. Data on gender impact has been required by the FDA only after 1993. The aim of this work was to assess the impact of gender and age on **pharmacokinetics**.

METHODS

A systematic **online literature research** was performed on usual platforms. 168 references could be evaluated.

RESULTS

Cytochrome P450 isoenzyme subfamilies comprised in the most used drug interaction table (i.e. Flockhart, retrieved from http://medicine.iupui.edu/clinpharm/ddis) are **1A2**, **2B6**, **2C8**, **2C9**, **2C19**, **2D6**, **2E1**, and **3A4/5/7**. Other isoenzyme subfamilies according to SuperCYP (http://bioinformatics.charite.de/supercyp), Drugbank (http://www.drugbank.ca), or Uniprot (http://www.uniprot.org) are not duly known in practical pharmacology, partly because of their predominant extrahepatic tissue specificity. However, their importance for local adverse reactions may be considerable. Of a total of 57 human isoenzymes CYP450, only 10 subfamilies are currently used by physicians and pharmacists as interaction references in the practice (Table 1).

Table 1: Human CYP450 isoenzymes

1A1	2A6	3A4	4A11	5A1	7A1	8A1	11A1	17A1	19A1	20A1	21A2	24A1	26A1	27A1	39A1	46A1	51A1
1A2	2A7	3A5	4A22		7B1	8B1	11B1						26B1	27B1			
1B1	2A13	3A7	4B1				11B2						26C1				
	2B6	3A43	4F2														
	2C8		4F3														
	2C9		4F8														
	2C11		4F11														
	2C18		4F12														
	2C19		4F22														
	2D6		4X1														
	2E1		4V2														
	2F1		4Z1														
	2J2																
	2R1																
	2S1																
	2U1																
	2W1																

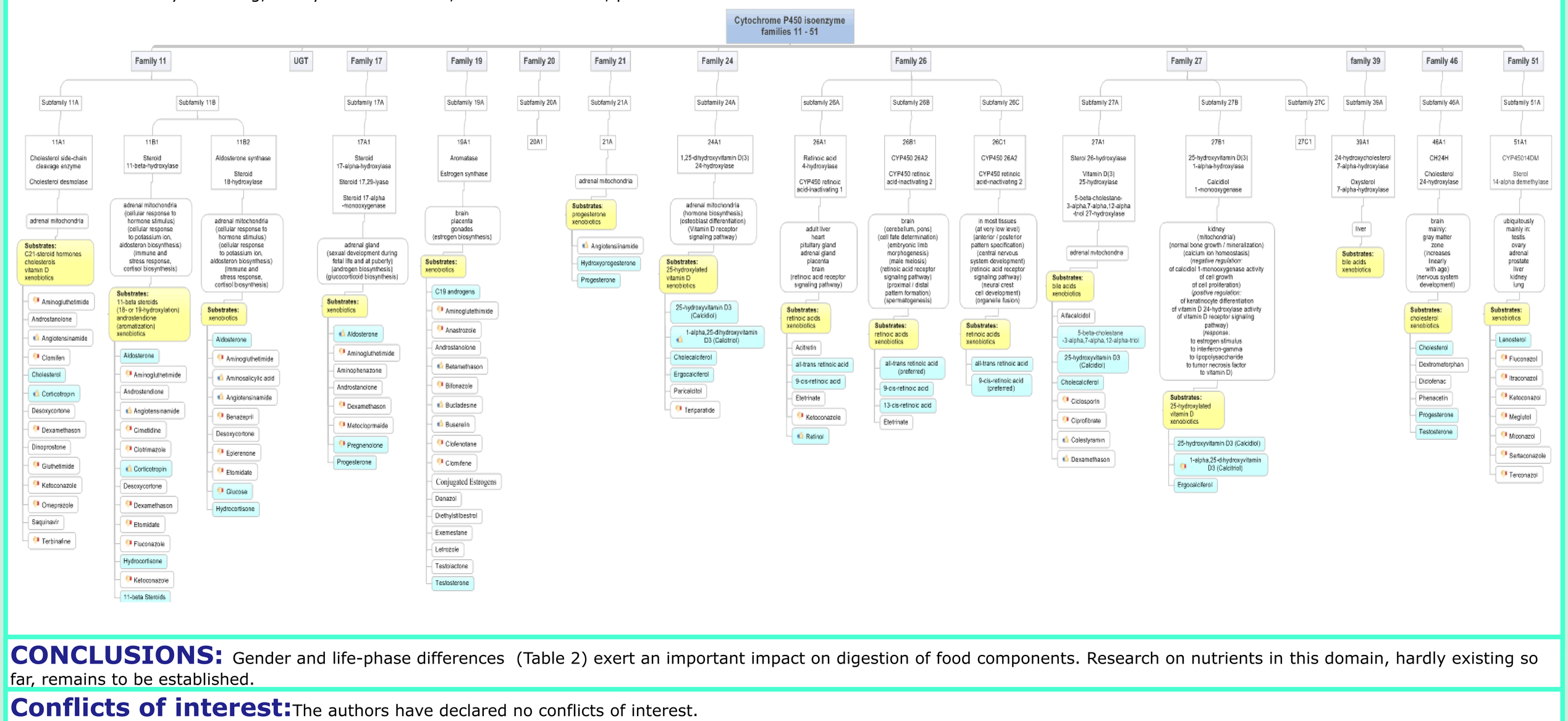
** Controversial reports arise from crossinfluences of co-localized P-gp and CYP3A4, 5, 7. Thus, only studies comprising drugs which are not transported by P-gp, are adequate in CYP3A4,5,7 studies and vice-versa.

Table 2: Examples of age & gender differences in pharmacokinetics

Age Group	Gender Differences	
Peri- and postnatal phase	No gender difference reported. CYP450 inducibility begins in the earliest embryonic stage and reaches high rates before birth. Drug disposition in newborns is low.	
Childhood	Iron anemia	Higher incidence in boys aged 11-15 (12.1%) than in equally aged girls (6.1%).
Adulthood	Mean gastric fasting pH	2.15 for men versus 2.8 for women, corresponding to a 5-fold H^+ activity in men. Facilitated amino acid assimilation in men.
	Gastrin and bicarbonate secretion	More constant level kept in men and secreted during substrate afflux in women.
	Gastric emptying and colon transit times	Longer in women (mainly in pregnancy). Regulation of motility by estrogen and progesterone.
	Efflux transporters, e.g. P-gp**	Expressed to a higher degree in men.
	Isoenzymes **CYP1A2**, **CYP2C9**, **CYP2E1**	Higher activity in men (CYP1A2 up to 40 fold).
	Isoenzymes **CYP3A4**,**5**,**7**, **CYP2A6**, **CYP2B6**, **CYP2D6**	More expressed in women. CYP2D6 however only in the fertile phase, and CYP3A4,5,7 depending on the menstrual cycle with top levels before ovulation and in pregnancy.
	Plasma levels of copper and ceruloplasmin	Contraceptives in women aged 20-39 increase plasma levels of copper and ceruloplasmin, but not its absorption.
	Copper absorption	Higher in women aged 20-59 (71%) than in men of the same age (64%). This difference does not exist in both genders aged 60-83.
	Protein digestion resistance	Protein digestion resistance due to PPI treatment in pregnancy is a documented risk factor of predisposition to immune responses and asthma of the child (5.6% versus 3.7% in the population). In pregnancy, trophokinetics change as a result of high progesterone levels, altered hemodynamics, cardiac output, etc.

Figure 1: CYP450 Isoenzymes Families 11-51

Cytochrome P450 isoenzyme families 11-51 as an extract of all 57 CYP450s featuring synonyms, tissue specificity, eventually biological function, and substrates. Green background: substrate is naturally occurring, no symbol: substrate, con icon: inhibitor, pro icon: inducer.



CONCLUSIONS: Gender and life-phase differences (Table 2) exert an important impact on digestion of food components. Research on nutrients in this domain, hardly existing so far, remains to be established.

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