Toxicokinetics - Variations due to Genetics or Interactions: Basics and Examples

Hans H. Maurer

Individual variations in the pharmacological or toxicological responses to the same drug dose may be caused by a variety of factors such as body mass, age, sex, kidney and liver function, drug-drug (food-drug) interactions, and genetic variability [1]. Detailed knowledge of the metabolism of drugs (of abuse) allows to predict possible interactions with other xenobiotics because of e.g. inhibition or induction of individual metabolic isoenzymes by poisons, drugs (of abuse), alcohol, tobacco smoke, or food ingredients [6, 12, 13]. This knowledge is a prerequisite for understanding pharmaco-/toxicokinetics and pharmacogenetic variations, for evidence-based case interpretation, for toxicological risk assessment, for developing toxicological analysis procedures, and for understanding pitfalls in drug testing.

The percentage of the isoforms of the main metabolizing phase I and phase II metabolism were summarized by Evans and Relling [2]. Substrates as well as relevant interactors (inhibitors and inductors) clinically important for pharmacokinetic and pharmacogenetic variations or interactions are summarized and actualized on http://medicine.iupui.edu/flockhart/clinlist.htm. Drug metabolism is largely determined by relevant genetic enzyme or transporter variants. The most important variants are the following polymorphically expressed proteins: the cytochrome P450 isoenzymes CYP2C9, CYP2C19, and CYP2D6, the alcohol/aldehyde dehydrogenase (ADH2, ALDH2), the phase II enzymes UDP-glucuronyltransferases (UGT1A1), thiopurin methyltransferases (TPMT), arylamine N-acetyltransferases (NAT2) and glutathione S-transferases (GSTM1, GSTT1), and finally transporters like P-glycoprotein [1].

In addition, also herbal remedies may produce interactions. Foti et al. for example could show, that in human liver microsomes, herbal drug mixture produced significant inhibition of multiple cytochrome p450 (P450) isoforms, including CYP2B6, CYP2C9, and CYP2D6. Based on the data presented, it is concluded that mixtures of herbal components may exhibit multiple modes of P450 inhibition, indicating the potential for complex herbal-drug interaction scenarios to occur [3].

The major metabolic pathways and the involved isoenzymes in humans are summarized in recent reviews for drugs of abuse and other drugs relevant in clinical and forensic toxicology [6, 9, 12, 13].

In case of relevant genetic variations, genotyping and phenotyping of the individuum should be performed. For example, Haertter et al. described an automated HPLC procedure for determination of dextromethorphan and its main metabolites in human plasma for in vivo phenotyping of CYP2D6 activity, which catalyzes the O-demethylation of dextromethorphan to dextrorphan [5]. For detection possible interactors, a systematic toxicological screening analysis (STA) should be performed [7, 8, 10, 11].

A nice example of the relevance of this issue in clinical and forensic toxicology is a case report on a life-threatening opioid intoxication developed in a patient after he was given small doses of codeine for the treatment of a cough associated with bilateral pneumonia [4]. Codeine is bioactivated by CYP3A4 into norcodeine and by CYP2D6 into morphine, which then undergoes further glucuronidation. CYP2D6 genotyping showed that the patient had three or more functional alleles, a finding consistent with ultra rapid metabolism of codeine. The authors attribute the toxicity to this genotype, in combination with inhibition of CYP3A4 activity by other medications and a transient reduction in renal function.

In conclusion, individual variations in the pharmacokinetic behavior of xenobiotics are of importance in therapeutic drug monitoring as well as in clinical and forensic toxicology, especially if pharmacokinetic calculations are used as basis for interpretation of analytical results. For example, the diazepam plasma concentration may be increased, if the CYP3A4 inhibitors ketoconazole or grapefruit juice were additionally taken in doses relevant for inhibition. The plasma concentrations of tricyclic antidepressants may also be increased if CYP2D6 inhibitors like paroxetine were taken or if the patient is a CYP2D6 poor metabolizer.

References

[1] Evans WE, McLeod HL (2003) Pharmacogenomics-drug disposition, drug targets, and side effects. N.Engl.J.Med. 348:538-549

[2] Evans WE, Relling MV (1999) Pharmacogenomics: translating functional genomics into rational therapeutics. Science 286:487-491

[3] Foti RS, Wahlstrom JL, Wienkers LC (2007) The in vitro drug interaction potential of dietary supplements containing multiple herbal components. Drug Metab Dispos. 35:185-188

[4] Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J (2004) Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N.Engl.J.Med. 351:2827-2831

[5] Hartter S, Baier D, Dingemanse J, Ziegler G, Hiemke C (1996) Automated determination of dextromethorphan and its main metabolites in human plasma by high-performance liquid chromatography and column switching. Ther.Drug Monit. 18:297-303

[6] Kraemer T, Maurer HH (2002) Toxicokinetics of amphetamines: Metabolism and toxicokinetic data of designer drugs, of amphetamine, methamphetamine and their N-alkyl derivatives [review]. Ther.Drug Monit. 24:277-289

[7] Maurer HH (2004) Position of chromatographic techniques in screening for detection of drugs or poisons in clinical and forensic toxicology and/or doping control [review]. Clin.Chem.Lab.Med. 42:1310-1324

[8] Maurer HH (2006) Hyphenated mass spectrometric techniques - indispensable tools in clinical and forensic toxicology and in doping control [review]. J.Mass Spectrom. 41:1399-1413

[9] Maurer HH, Kraemer T, Springer D, Staack RF (2004) Chemistry, Pharmacology, Toxicology, and Hepatic Metabolism of Designer Drugs of the Amphetamine (Ecstasy), Piperazine, and Pyrrolidinophenone Types, a Synopsis [review]. Ther.Drug Monit. 26:127-131

[10] Maurer HH, Peters FT (2005) Towards High-throughput Drug Screening Using Mass Spectrometry. Ther.Drug Monit. 27:686-688

[11] Maurer HH, Pfleger K, Weber AA (2007) Mass Spectral and GC Data of Drugs, Poisons, Pesticides, Pollutants and their Metabolites. Wiley-VCH, Weinheim

[12] Maurer HH, Sauer C, Theobald DS (2006) Toxicokinetics of Drugs of Abuse: Current Knowledge of the Isoenzymes Involved in the Human Metabolism of Tetrahydrocannabinol, Cocaine, Heroin, Morphine, and Codeine [review]. Ther.Drug Monit. 28:447-453

[13] Staack RF, Maurer HH (2005) Metabolism of Designer Drugs of Abuse [review]. Curr.Drug Metab. 6:259-274

Univ.-Prof. Dr. Dr. h.c. Hans H. Maurer
Department of Experimental and Clinical Toxicology
Institute of Experimental and Clinical Pharmacology and Toxicology
Saarland University
D-66421 Homburg (Saar)
E-mail: hans.maurer@uniklinikum-saarland.de