

## PHARMACOGENETICS AND INTERACTIONS OF ANTIDEPRESSANTS IN THE TREATMENT OF CO-MORBID ILLNESS

Alma Mihaljević-Peješ<sup>1</sup>, Marina Šagud<sup>1</sup>, Nada Božina<sup>2</sup>, Maja Živković<sup>3</sup> & Nikolina Jovanović<sup>1</sup>

<sup>1</sup> University Department, Clinical Hospital Zagreb, Kišpatičeva 12, Zagreb, Croatia

<sup>2</sup> Clinical Hospital Centre Zagreb, Clinical Institute of Laboratory diagnostic, Kišpatičeva 12, Zagreb, Croatia

<sup>3</sup> Neuropsychiatric Hospital "Dr Ivan Barbet", Popovača, Croatia

### SUMMARY

Patients who require long-term treatment for depression have an increased risk of experiencing drug interactions since they will take medications for intercurrent and/or co-morbid illness. Antidepressants can be the object of drug interactions by other substances, or they can precipitate interactions by inhibiting enzyme pathways. There is an increasing agreement about the importance of polymorphisms in cytochrome P450 enzymes and the effects of drug-drug interactions in relation to the incidence of adverse effects. Genetic test suitable for the routine laboratory are now available for some important metabolizing enzymes (e.g. CYP2D6, CYP2C19) identifying those individuals who are slow or fast metabolizers of certain drugs. Specific antidepressants differ in the interactions with CYP450 isoenzymes and in their susceptibility to drug-drug interactions.

The main focus of this article is pharmacokinetic drug interactions of antidepressants. With that specific knowledge, clinicians can improve outcomes of depressed patients, by considering the possibility of drug interactions both before prescribing a specific antidepressant and while monitoring for response, adverse effects and patient compliance.

**Key words:** CYP450 isoenzymes – antidepressants - drug-drug interactions

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### INTRODUCTION

Clinically important drug interactions are defined as events in which the safety or effectiveness of a drug is modified by a second substance. The second substance may be a concomitantly prescribed drug, or over-the-counter medication, or some other substance such as food, alcohol or tobacco smoke (Ereshefsky & Dugan 2000). Many drug interactions are pharmacokinetic rather than pharmacodynamic interactions. The pharmacokinetic drug interactions of antidepressants is very complex topic. Drug interactions can lead to serious, even fatal, drug adverse effects. In a study of 1000 hospitalized elderly patients, adverse events from drug interactions were responsible for hospitalization in 11.5% of the patients (Doucet et al. 1996). In the other hand, clinicians sometimes take advantage of therapeutic drug interactions, in which the addition of a second drug enhances the efficacy of the first.

### PHARMACOKINETIC DRUG INTERACTIONS

There are two kinds of drug interactions. One is pharmacodynamic, the second is pharmacokinetic. In this article we shall be focused on pharmacokinetic drug interactions. Pharmacokinetic drug interactions occur when a drug's absorption, distribution, metabolism or excretion are changed by another drug or substance. Elimination of drugs occurs through two phases of metabolism. In phase I reactions convert the parent drug to metabolites through oxidation, reduction or hydrolysis. In phase II reactions are conjugation in which metabolites with endogenous substances leave inactive compounds for eventual excretion (Richelson 1997).

There are several levels about we should take care during antidepressant therapy. Specific antidepressants differ in the interactions with CYP450 isoenzymes and in their susceptibility to

drug-drug interactions. The drug can be a substrate, binding to the CYP450 isoenzymes and being metabolized and/or the CYP450 isoenzymes can be competitively blocked by the drug (Ereshefsky 2001). Some substances can also induce enzymes gene expression (Ereshefsky 2001).

CYP enzymes show large interindividual differences in activities due to genetic variants constituting multiallelic systems. These can be distinguished as poor, intermediate, extensive or ultra fast metabolizers (Bondy & Spellmann 2007). Clinically relevant polymorphisms have been documented for CYP2D6, CYP1A2 and CYP2C9 and CYP2C19. A poor metaboliser and patient taking a potent CYP450 inhibitor will have same phenotype for the metabolism of co administered drug. Therefore, both genetic and drug interactions will result in high levels of drug remaining in the blood for long time period.

We should also emphasize that ethnicity and widely varying polymorphism frequencies observed in CYP450 isoenzymes play important role for drug safety and dosage.

There are three main points for understanding drug interactions. First, pharmacokinetic drug interactions are potential and not a certain problem. Second, these interactions are more likely to occur with high-risk drugs (e.g. fluvoxamine (CYP1A2), fluoxetine and paroxetine (CYP2D6) and nefazodone (CYP3A4)). Third, interactions are unlikely to occur with low-risk drugs (e.g. sertraline, venlafaxine, bupropion and mirtazepine) but they still can occur (Richelson 1998).

## CONCLUSION

The nature of drug response is highly complex, involving genetic and environmental factors. Because of these factors there are much interindividual variabilities in treatment with

antidepressants (Mihaljević-Peješ et al. 2008). Most of new antidepressants (SSRIs, SNRIs and others) interact with the CYP450 enzymes and are susceptible to drug-drug interactions to varying degree. When prescribing an antidepressant it is important to consider how it affects the metabolism of other drugs and how other drugs affect its metabolism.

With that specific knowledge, clinicians can improve outcomes of depressed patients, before prescribing a specific antidepressant and while monitoring for response, adverse effects and patient compliance (Ereshefsky et al. 2005).

## REFERENCES

1. Bondy B and Spellmann I.: *Pharmacogenetics of antipsychotics: Useful for the Clinician?* *Curr Opin Psychiatry*. 2007; 20:126-130.
2. Doucet J, Chassagne P, Trivalle C, et al. *Drug-drug interactions related to hospital admissions in older adults: a prospective of 1000 patients.* *J Am Geriatr Soc* 1996; 44:944-8.
3. Ereshefsky L. *Antidepressant drug interaction considerations.* *Manag Care* 2001 Aug; 10 (8 Suppl.): 10-3.
4. Ereshefsky L., Dugan D. *Review of the pharmacokinetics, pharmacogenetics, and drug interaction potential of antidepressants: focus on venlafaxine.* *Depress Anxiety* 2000. 12: Suppl. 1:30-44.
5. Ereshefsky L., Stanford J, Grothe D. *Antidepressant Drug-Drug Interaction Profile Update.* *Drugs R D* 2005; 6:323-336.
6. Mihaljević-Peješ A., Šagud M., Božina N., Živković M.: *Pharmacogenetics and antidepressant treatment in integrative psychiatry perspective.* *Psychiatria Danubina*, 2008; 20:355–355.
7. Richelson E. *Pharmacokinetic drug interactions of new antidepressants: a review of the effects on the metabolism of other drugs.* *Mayo Clin Proc* 1997; 72:835-47.
8. Richelson E. *Pharmacokinetic interactions of antidepressants.* *J Clin Psychiatry* 1998. 59:suppl. 10:22-26.

### Correspondence:

Alma Mihaljević-Peješ  
Clinical Hospital Centre Zagreb  
Kišpatičeva 12, 10000 Zagreb, Croatia, Croatia  
E-mail: apeles@mef.hr