Toxicological aspects in relation to the drug transporter P-glycoprotein at the blood-brain barrier

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In recent years there has been increasing focus on the role of the drug transporter P-glycoprotein (P-gp) with regard to drug penetration into the brain. Being located at the blood-brain barrier (BBB), P-gp actively pumps drugs out of the brain, and studies in P-gp knockout mice have revealed that P-gp can have a profound effect on the ability of some drugs to enter the brain. Important examples are cardiovascular drugs (digoxin, quinidine), opioids (morphine, loperamide, methadone), HIV protease inhibitors, the new generation of antihistamines, and some antidepressants and antipsychotics. Case reports and controlled studies in humans have suggested that genetic variation and drug-drug interactions in relation to P-gp may be of toxicological relevance for some opioids, antidepressants and antipsychotics. These findings are supported by experimental data. Concerning antipsychotics, risperidone and its active metabolite, 9-HO-risperidone, are strongly influenced having more than 10 times higher cerebral concentration in P-gp knock-out mice than in control mice [1]. Taking into account that polytherapy is commonplace in psychiatry, theoretically there is a risk of drug-drug interactions with regard to P-gp at the BBB. Administration of the strong P-gp inhibitor cyclosporine A in a high concentration can increase the cerebral concentrations of risperidone and 9-HO-risperidone (active moiety) by 40% [1]. Analogously, cyclosporine A administration was able to increase the cerebral nortriptyline concentration by about 30% [2]. Another strong P-gp inhibitor, verapamil, was able to increase the cerebral nortriptyline concentration by 60%, which was of the same order of magnitude as observed in knockout mice. Thus, the impact of verapamil corresponded to complete inhibition of P-gp [3]. Co-administration of risperidone and nortriptyline in therapeutically relevant doses, on the other hand, did not result in significant perturbations of the brain – blood concentration ratios [1, 2].
In conclusion, further studies on the possible impact of drug-drug interactions in relation to P-gp would be desirable to evaluate the toxicological implications.

REFERENCES:

1 Ejsing TB, Pedersen AD, Linnet K. P-glycoprotein interaction with risperidone and 9-OH-risperidone studied in vitro, in knock-out mice and in drug-drug interaction experiments. Hum Psychopharmacol 2005; 20: 493-500.

2 Ejsing TB, Linnet K. Influence of P-glycoprotein inhibition on the distribution of the tricyclic antidepressant nortriptyline over the blood-brain barrier. Hum Psychopharmacol 2005; 20: 149-153

3 Ejsing TB, Hasselstrom J, Linnet K. The influence of P-glycoprotein on cerebral and hepatic concentrations of nortriptyline and its metabolites. Drug Metabol Drug Interact 2006; in press.

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