An experimental study on the pharmacokinetics of psychotropic drugs with focus on the role of the drug transporter P-glycoprotein

Thomas Broeng Ejsing, MSc

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Official opponents: Flemming Bach, Kim Dalhoff, and Per Plenge.

Supervisors: Kristian Linnet and Raben Rosenberg

Correspondence: Thomas Broeng Ejsing, MSc, PhD, Skejby Vænge 113C, 8200 Århus N, Denmark

e-mail: deshret@hotmail.com

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ABSTRACT

This study focused on the influence of the drug transporter P-glycoprotein on the distribution between blood and brain of the atypical antipsychotic drug risperidone and the tricyclic antidepressant nortriptyline. The aim was to establish whether there is a risk for P-glycoprotein mediated drug-drug interaction between psychotropic drugs at the blood-brain barrier. The main results were:

1. Risperidone, its active metabolite (9-OH-risperidone), and nortriptyline were able to stimulate P-glycoprotein-mediated ATPase activity in vitro showing that these drugs are P-glycoprotein substrates.
2. Administration of nortriptyline to P-glycoprotein knock-out mice led to brain/serum concentration ratios that were on average xx1.7 times higher than those of the wild-type mice.
3. Administration of risperidone to P-glycoprotein knock-out mice gave brain/serum concentration ratios that were on average 12 times higher than those of the wild-type mice. Thus P-glycoprotein may be partly responsible for the relatively low brain concentration of risperidone.
4. Interaction studies in rats showed that high doses of the potent P-glycoprotein inhibitors cyclsporine A and verapamil gave 50 and 100% inhibition of P-glycoprotein-mediated transport, respectively.
5. Interaction studies between risperidone and nortriptyline (administered in doses yielding serum concentrations corresponding to the therapeutic levels in humans) gave no significant changes in the concentration gradients over the blood-brain barrier.

In conclusion, P-glycoprotein-mediated drug-drug interactions over the blood-brain barrier between psychotropic drugs and P-gp inhibitors are observed when the latter are administered in high doses. When the psychotropic drugs were administered in clinically relevant doses, no drug-drug interactions could be detected. The experiments suggest that the risk for clinically relevant drug-drug interactions between psychotropic drugs with regard to P-glycoprotein is limited.