S28-02 - **IMPACT OF GENE POLYMORPHISMS ON PHARMACOKINETICS AND PHARMACODYNAMICS OF OLANZAPINE AND CLOZAPINE**

M.-L. Dahl[1,2]

[1]Dept of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, [2]Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden

Treatment with antipsychotic drugs is, despite the introduction of many new compounds, far from optimal in a large proportion of patients. Apart from lack of or insufficient response, various adverse drug reactions often limit the use of otherwise efficient drugs, and increase the risk of non-compliance and poor treatment outcome. Thus, there is considerable need for individualized treatment in order to maximize the therapeutic outcome. This variability in drug response may be related to both pharmacokinetic and pharmacodynamic factors, many of which are genetically regulated. In the presentation, the contribution of allelic variability in genes coding for drug metabolic enzymes *(CYP2D6*, *CYP1A2* and others*)* and transport proteins *(ABCB1)*, as well as drug targets, to the pharmacokinetics and clinical effects of atypical antipsychotics will be discussed, using olanzapine and clozapine as model drugs. While *CYP2D6* had no influence, carriage of two *CYP1A2* allelic variants was associated with higher dose-adjusted plasma concentrations of clozapine and its metabolite desmethylclozapine. Patients with elevated insulin levels more frequently carried the **1C* and **1D* alleles, had higher plasma drug levels, higher blood lipids and HOMA-IR compared to patients with normal insulin levels. Associations were found between *HTR2C* and *HTR2A* haplotypes and increased BMI and C-peptide levels. A *HTR2C* haplotype was also shown to be significantly more frequent among obese than non-obese patients on long-term clozapine treatment. The data illustrate the need of an integrated approach involving both pharmacokinetic and -dynamic aspects in pharmacogenetic studies aiming at personalized antipsychotic treatment.

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