Oral

[O25-2] O25-2: CNS and miscellaneous

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[O25-2-2] Correlation between serum concentrations of clozapine, N-desmethylclozapine and ABCB1 genotype on neutrophil granulocyte count in schizophrenia patients

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Background

Clozapine is by far the most effective atypical antipsychotic drug in treatment of schizophrenia. However, the therapeutic use of clozapine is limited by serious side effects, including drop in neutrophil granulocyte count (ANC), which may result in agranulocytosis (i.e. ANC <0.5x10^9cells/L). The mechanism of clozapine-induced granulocyte toxicity is still poorly understood, but might be related to systemic or local exposure of clozapine and/or metabolites. The aim of present study is to investigate the impact of serum concentrations of clozapine and N-desmethylclozapine, as well as genetics encoding the granulocyte-located efflux transporter P-glycoprotein (*ABCB*), on ANC in clozapine-treated patients.

Methods

The study included 71 Caucasian patients with available daily clozapine dose, steady state serum trough concentrations of clozapine and N-desmethylclozapine, *ABCB1* genotypes/haplotypes and ANC. The number of observations per patient varied from 1 to 69, and the correlations of clozapine and N-desmethylclozapine concentrations, and *ABCB1* haplotype (i.e. *ABCB1 *1/*1 vs. *2/*2*), with ANC were analyzed using linear-mixed model.

Results

Of the included patients, 19 were homozygous carriers of the *ABCB1 *2* haplotype, while the remaining were *ABCB1 *1* carriers. A total number of 450 ANC measurements were included in the statistical analysis. Increasing age and N-desmethylclozapine concentration were positively associated with ANC, and estimated slopes in the final mixed model analysis were 0.04 x 10^9cells/L/year (95% confidence interval (CI): 0.01-0.07, p<0.001) and 0.0009 x 10^9cells/L/nM (95% CI: 0.0006-0.0012; p<0.01), respectively. *ABCB1* haplotype, clozapine concentration and gender were not significantly associated with ANC (p>0.4).

Conclusions

The present study shows that N-desmetylclozapine, the main clozapine metabolite, is positively correlated with ANC in patients with schizophrenia. Although the mechanistic explanation of clozapine-induced granulocyte toxicity needs further research, this finding might indicate that high formation of N-desmethylclozapine counteracts generation of other clozapine metabolites mediating neutrophil granulocyte toxicity. Finally, our study provides no evidence that *ABCB1* genetics is of importance for ANC.