Symposium

[S-12] S-12: TDM for central nervous system drugs

Chairs: Kiyofumi Yamada, Japan / Philip Nicholaou Patsalos, UK
Tue. Sep 26, 2017 10:30 AM - 12:00 PM Room E (1F)

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[S-12-3] Lamotrigine and valproate drug interactions —the role of pharmacogenomics

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Background
For the treatment of epilepsy anticonvulsants are often used as polytherapy. UDP-glucuronosyltransferase enzymes (UGTs) and some ABC transporters are involved in lamotrigine and valproic acid glucuronidation and transport, and these drugs are commonly administered in combination. The aim of the proposed research was to investigate the role of UGTs and ABCs transporter polymorphisms in interindividual variability of lamotrigine and valproate bioavailability.

Methods
A total of 205 patients were enrolled, 131 treated with lamotrigine alone and 74 treated with lamotrigine and valproate. Determination of drug concentrations was performed by HPLC with diode array detector for lamotrigine and by immunoassay method for valproate. Genotyping of *UGT2B7* -161C>T, *UGT1A4* 142T>G, *UGT1A4* 70C>A, *ABCB1 1236C>T, ABCG2*421C> A was performed by *real time PCR* method, using *TaqMan* assays.

Results
Lamotrigine trough concentrations, adjusted for age, sex, body mass index, dose, were around 2.4-fold higher in patients co-treated with valproate. There was no overall effect of variant allele of *UGT2B7* -161C>T, *UGT1A4* 142T>G and *UGT1A4* 70 C>A on either lamotrigine or valproate trough or trough/dose corrected concentrations. *ABCB1* 1236C>T genotypes also has no effect on lamotrigine and valproate concentrations. *ABCG2* 421C>A genotypes has no overall effect on either lamotrigine (adjusted GMR 1.12, p=0.285) or valproate trough concentrations (adjusted GMR 1.17, p=0.370), but there appeared a significant interaction between A-allele carriage in lamotrigine-valproate-treated subjects. *ABCG2* 421A-allele carriage (vs. CC) was associated with 61% higher lamotrigine trough (p=0.019), whereas in lamotrigine-only-treated subjects, A-allele carriage was associated with somewhat lower trough (vs. CC; GMR=0.80, p=0.085) indicating a significant (p=0.004) two-fold difference in A-allele effect between treatment subsets.

Conclusions
Our study did not confirm influence of *UGT2B7, UGT1A4 and ABCB1* gene polymorphisms on lamotrigine trough plasma concentrations. Valproate was associated with significantly higher lamotrigine troughs regardless of the *ABCG2* genotype, but the effect appeared two-fold higher in *ABCG2* 421 A-allele carriers (GMR 4.29) than in 421CC-subjects (GMR 2.15). The role of *ABCG2* genotype still needs to be confirmed in a larger polytherapy group.