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ABSTRACTS VOLUME

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INFLUENCE OF CYP2C9 POLYMORPHISM ON SERUM LEVELS OF PHENORBABITAL METABOLITES

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Background: Genotype-phenotype relationship in epilepsy is fairly complex but studies have shown involvement of genetic factors affecting pharmacocinetics of the AEDs (antiepileptic drugs). One of the most widely used antiepileptic drugs is phenobarbital (PHB), the majority of PHB is metabolized by CYP2C9 in the liver to form an inactive metabolites, p-hydroxy-phenobarbital. Genetics polymorphisms of CYP2C9 may affect the inter-individual differences in drug metabolism. Subjects with the CYP2C9*2 allele are low-metabolizers and therefore could require a lower dose of the drug. The aim of the study is to evaluate the association between CYP2C9 polymorphism and phenobarbital metabolism in subjects with epilepsy.
Method: We studied 36 epileptic patients (29 males; age 40±11.7 years) under maintenance PHB therapy and the most common AEDs (72% Carbamazepine, 28% Valproate, 11% Primidone, 6% Phenytoin, 33% Levetiracetam, 11% Lamotrigine). The mean dosage of PHB was 2.13 ± 0.80 mg/kg. Total genomic DNA was extracted from whole blood by commercial kit (Roche). CYP2C9*2 430C>T allelic discrimination was performed by PCR-RFLP. The dosage of PHB was performed in a fasting state and after 4h from the administration of the drug to evaluate the conversion of PHB into its metabolite. Serum dosage of PHB was performed by HPLC with isocratic elution on a C18 column (Sigma) and UV detection at 220 nm.
Results: Among the study group, 89% were CYP2C9 430CC, 11% were heterozygous 430CT and no homozygous were identified. The fasting mean value of PHB in non carriers and carriers of the variant allele was 24.18 ± 7.67 and 20.42 ± 4.49 mcg/mL respectively; after 4h the mean value were 25.31 ± 8.68 and 20.20 ± 6 mcg/mL, in the two groups. When we compare the variation of PHB after 4h among the non carriers group and the carriers one, we didn't find statistical significant differences (P >0.05).
Conclusions: From the results obtained, we assume that the serum values of PHB, instead of CYP2C9*2 variant, could be influenced by AEDs as Lamotrigine and Valproate that are inhibitor of CYP2C9. The major limits of the present study is the low number of patients; moreover clinical and pharmacological variables could interfere with PHB pharmacocinetics.

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META-ANALYSIS OF THE EFFECT OF THE POLYMORPHISM OF DONORS AND RECIPIENTS CYP3A5 GENE ON TACROLIMUS PHARMACOKINETICS IN LIVER TRANSPLANTATION

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Background: Tacrolimus is one of the most commonly immunosuppressants used in organ transplant. Its pharmacokinetic is highly variable so there is risk of administering doses inappropriate and suffer secondary consequences as graft rejection or toxicity. One factor that contributes to this is the polymorphism of its metabolizing enzyme CYP3A5. Studies evaluating the association between variants non-expresser (CYP3A5 * 3) and tacrolimus blood levels are discordant on stage liver transplantation, which has led to a lack of consensus on its usefulness. We aim is making a meta-analysis of published studies about the effect of polymorphism of the donors and recipients CYP3A5 6986A>G gene on tacrolimus pharmacokinetics in liver transplantation.
Methods: Selection criteria: cohort studies that evaluated the relationship between polymorphism of CYP3A5 of donors and recipients of liver transplantation and tacrolimus blood concentration weighted by the daily dose per kilogram body weight (C/D) until one year after transplantation. There was no restriction by age, language or publication status. Search strategy and selection: A literature search was performed up to March 2012 by using the Cochrane Library, MEDLINE, EMBASE and grey literature. Data analysis. Data were pooled (random effects model) and the results expressed as mean difference (MD) of the C/D and corresponding 95% confidence interval.
Results: Seven studies involving donors (316 patients) and five recipients (469 patients). The meta-analysis demonstrated that, in donors, the C/D ratio was significantly higher in patients with non-expresser polymorphism in all periods, but the quality of the evidence was adequate only for the first month. In recipients, the type of polymorphism did not influence on C/D ratio, but the quality of evidence was low.
Conclusion: In donors, the polymorphisms of CYP3A5 6986A>G affects the pharmacokinetics of tacrolimus. In recipients it has no effect, but the quality of the evidence is not conclusive.