ROLE OF POLYMORPHISMS OF THE UGT1A9 GENE IN COMT INHIBITOR-INDUCED HEPATOTOXICITY IN PARKINSON'S DISEASE: A CLINICAL STUDY

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Introduction. Entacapone and tolcapone are catechol-*O*-methyltransferase (COMT) inhibitors used for the treatment of Parkinson's disease (PD). Tolcapone, the first to be marketed, was withdrawn from the European Union and Canada, and restricted in the United States, due to severe hepatotoxicity, while entacapone is regarded as safer, although some cases of entacapone-induced hepatotoxicity have been described. In Europe, tolcapone has been recently reintroduced, however restricted to prescription by physicians experienced in the management of PD and with the recommendation that liver function tests be carried out on a regular basis as long as the drug is used. Both tolcapone and entacapone are almost completely eliminated through biotransformation. The most important metabolic pathway for both compounds is glucuronidation through UDP-glucuronosyltransferase (UGT) 1A9, and we previously reported two cases of COMT inhibitor induced asymptomatic hepatic dysfunction associated with functionally defective mutations of the UGT1A9 gene (1).
Aims. To investigate associations between functionally defective allelic variants of UGT1A9 with the occurrence of hepatic toxicity in PD patients treated with COMT inhibitors.
Methods. In a prospective study we are currently enrolling PD patients treated with COMT inhibitors. Hepatic toxicity is assessed by laboratory monitoring of liver enzymes. Genotyping of UGT1A9 is performed by direct sequencing of the PCR amplification of DNA obtained from whole blood samples.
Results. At present, february 2007, the study has enrolled 50 patients (F/M = 18/32) on entacapone. Two of these patients have previous history of hepatic dysfunction chronologically related to entacapone administration. Genotyping has shown that in both cases the promoter region of the UGT1A9 gene is A(T)9AT, which results in lower trascriptional activity and, in one case, the 5'-region of exon 1 carries the nonsynonymous SNP UGT1A9*3, which results in a decrease of glucuronidation activity.
Conclusion. Preliminary data further support the hypothesis that UGT1A9 poor metabolizer genotype(s) is (are) a risk factor for hepatic dysfunctions induced by COMT inhibitor. Final assessment of the association will be possible upon completion of the study.
1.Martignoni E, Cosentino M, Ferrari M, Porta G, Mattarucchi E, Marino F, Lecchini S, Nappi G (2005) Neurology. 65(11):1820-2.