IMPACT OF *CYP3A4* AND *CYP3A5* POLYMORPHISMS ON CLINICAL OUTCOME OF DONEPEZIL IN ALZHEIMER'S DISEASE PATIENTS

T. PAOLETTI[1], M.G. SCORDO[2], G. MIGLIO[1], M.L. VILLA[3], M.L. DAHL[2], G. LOMBARDI[1]

[1] DISCAFF Department, University of "Piemonte Orientale Amedeo Avogadro", Novara, Italy;
[2] Department of Medical Sciences, Clinical Pharmacology, Uppsala University Hospital, Uppsala, Sweden; [3] Geriatric Clinical Unit, " Ospedale Maggiore della Carità", Novara, Italy

Donepezil is a selective acetylcholinesterase inhibitor widely used in the symptomatic treatment of mild to moderate Alzheimer's disease (AD), providing benefits in cognition, global functions and activities of daily living in AD patients. There is an high degree of variability in the clinical efficacy, safety and tolerability of donepezil among patients, that might be due, at least partially, to genetically determined variations in the patient metabolic capacity. Donepezil is extensively metabolized by hepatic microsomial cytochrome P450 (CYP) enzymes, mainly CYP3A4 and CYP2D6 with a minor contribution of CYP3A5, CYP3A7 and CYP3A43.
Since polymorphic sites in the regulatory regions of *CYP2D6, CYP3A4* and *CYP3A5* have been demonstrated, the aim of our study was to determine the impact of the *CYP3A4/CYP3A5* polymorphism on kinetics and clinical outcome of donepezil therapy.
45 patients (36 women and 9 men, aged 61-93 years) with diagnosis of probable mild-to-moderate AD (NINCDS-ADRDA *Work group criteria*), in therapy with donepezil (5 or 10 mg/day), since at least 3 months, were enrolled in the study. Before starting therapy a clinical evaluation with international scales (MMSE, IADL, ADL, ADAS-cog, CIBIC-plus) was performed.
*CYP3A4*1B*, **3* and **4* detrimental alleles, as well as *CYP3A5*2* and **6* alleles, have been identified by allele-specific PCR followed by digestion with restriction enzymes, while the presence of the *CYP3A5*3* allele was investigated by TaqMan™ allelic discrimination. Donepezil steady-state plasma concentrations were measured by HPLC method.
Six patients were heterozygous for *CYP3A4* (*CYP3A4*1/*1B*, n=2; *CYP3A4*1/*4*, n=4), while 8 subjects carried one functional *CYP3A5*1* allele (*CYP3A5*1/*3*). No statistically significant correlation was found between *CYP3A4/CYP3A5* genotypes and plasma donezepil concentration, nor between genotypes and clinical responses (as measured by change in MMSE scores).
Although the limited number of subjects involved in our pilot study does not allow definite conclusions to be drawn, our data suggest that the *CYP3A4/CYP3A5* polymorphisms are unlikely to influence donepezil metabolism and/or clinical outcome.