Predicting steady state donepezil plasma concentrations in patients with Alzheimer disease through clinical characteristics and hepatic cytochrome phenotype

F. Groppa[1], S. Granziera[2], A. Coin[2], G. De Rosa[1], L. Bertolaso[3], M. Gusella[3], M. De Rui[2], A. Girardi[2], M.V. Pamio[2], G. Sergi[2], E. Manzato[2], R. Padrini[1]

[1] Clinical Pharmacology Unit, Dept. of Medicine, University of Padova, Padova.

[2] Geriatric Clinic, Dept. of Medicine, University of Padova, Padova.

[3] Laboratory of Pharmacology and Molecular Biology, Trecenta S.Luca Hospital,

Dept. of Oncology - Azienda ULSS 18 – Rovigo.

Donepezil (D), an acetylcholinestherase inhibitor, is currently used for the treatment of mild-to-moderate Alzheimer disease (AD). It is metabolized by cytochromes CYP3A4 and CYP2D6 to 4 major metabolites, two of which are active. D is also a substrate of the P-glycoprotein (P-gp). A correlation has been demonstrated between D plasma levels and clinical response and a therapeutic range between 30 and 70 ng/mL has been suggested. The aim of our study was to establish which demographic and pharmacological factors can predict D plasma levels during chronic treatment.

METHODS.

Thirty patients with mild-to-moderate AD, on stable D treatment for at least three months (10mg daily, at 8 p.m.) gave their written informed consent and were studied. On the first planned visit (at 8-9 a.m.) relevant clinical characteristics and ongoing therapies were recorded and a blood sample was drawn to measure plasma concentrations of the drug and 3 its metabolites [6-O-desmethyl-donepezil (6-DD), 5-O-desmethyl-donepezil (5-DD), and donepezil-N-oxide (D-ox)], using a new HPLC method set up in our lab. In addition, the activities of CYP3A4 and CYP2D6 have been determined by administering omeprazole (OME, 20mg, p.o.) and dextromethorphan (DMT, 15mg, p.o.) and by measuring the ratio between plasma concentrations of OME and omeprazole sulphone (SULF) 3 hours after dosing (as a marker of CYP3A4 activity) and the ratio between DMT and dextrophan (DOR) urine concentrations in urine collected for 8-hour (as a marker of CYP2D6 activity).

RESULTS

Mean patients' age was 81± 8 yrs (range: 70-92); 9 were males and 21 females and 16 of them were taking drugs known to be substrates or inhibitors of CYP3A4 and/or P-gp (atorvastatin, simvastatin, quetiapine, trazodone, paroxetine, sertraline, verpamil). Mean plasma concentrations (± s.d.; range) of D and its main metabolites were as follows : D = 53.7 ng/mL (± 20.5; 25-106); 6-DD = 9.0 ng/mL (± 10.4; 0.13-36.0); 5-DD = 0.52 ng/mL (± 0.55; 0.11-2.7); D-ox = 6.1 ng/mL (± 9.1; 0.52-45.4). Univariate analysis showed that patients taking substrates/inhibitors of CYP3A4 or P-gp had higher D concentrations (58.1 ng/mL vs 38.4 ng/mL; $p = 0.014$) and lower D-ox concentrations (3.7 ng/mL vs 10.3 ng/mL; $p = 0.053$) than patients who did not. Furthermore, a significant correlation was found between D concentration and age ($r^2 = 0.30$; $p = 0.0019$), and between D concentration and CYP2D6 activity (measured as DMT/DOR metabolic ratio; $r^2 = 0.14$; $p = 0.044$). Gender and CYP3A4 activity (OME/SULF metabolic ratio) did not showed any correlation with drug or metabolite concentrations. Multivariate regression analysis including as independent variables co-administration of interacting drugs, age and CYP2D6 activity showed a significant correlation with D concentrations ($r^2 = 0.49$; $p = 0.00065$), with a mean prediction error of 23.1 ± 11.5 %.

DISCUSSION.

Plasma concentrations of D and its metabolites showed a wide inter-subject variability. Of the two active metabolites (6-DD and 5-DD) 6-DD had plasma levels ≈ 20% of those of the parent drug and may partially contribute to D effect. Instead, plasma concentrations of 5-DD were extremely low in our patients. Uni- and multivariate analyses identified age, CYP2D6 activity and co-administration of potentially interacting drugs as predictors of steady state D concentrations explaining ≈ 50% of variability. Patients' enrolment is still ongoing and if these preliminary results will be confirmed at the conclusion of the study, it would be possible to anticipate the true exposure of patients to the drug during chronic treatment and to personalize the initial D dose before starting drug therapy.