ABSTRACT

Introduction: The human cytochrome P450 2D6 (CYP2D6) is involved in the oxidative metabolism of about 25 % of all commonly prescribed drugs. It is characterized by high range of interindividual variability due to both environmental and genetic factors. The ability to measure the activity of CYP2D6 enzyme is of high significance. Genotyping alone is not sufficient to accurately predict an individual´s actual CYP2D6 activity, phenotyping on the other hand can determine the exact enzymatic activity as it also reflects non-genetic factors. Beta-blocker agent metoprolol undergoes extensive pre-systemic elimination, with enzyme CYP2D6 accounting for about 70 to 80 % of its metabolism. Metoprolol also serves as one of the probe drugs of CYP2D6. The metabolic ratio of metoprolol over its metabolite α-hydroxymetoprolol in plasma 3 hours after metoprolol administration is used for the measurement of CYP2D6 enzyme activity.

Aims: To compare CYP2D6 metabolic activity after first metoprolol dose and in steady state. Further to investigate the influence of CYP2D6 activity on metoprolol pharmacokinetics and pharmacodynamics in patients on metoprolol therapy.

Methods: Thirteen adult hypertensive patients in whom an introduction of beta-blocker metoprolol was indicated were included for comparison of CYP2D6 activity after first metoprolol dose and in steady state. Blood samples were drawn after first dose and at least 2 weeks since metoprolol introduction to ensure steady state. The influence of CYP2D6 activity on metoprolol disposition was studied in forty-nine patients. Serum metoprolol and α-hydroxymetoprolol concentrations, resting heart rate were measured before, 1, 3 and 4 hours post-dose. Metoprolol and α-hydroxymetoprolol serum concentrations were measured by high – performance liquid chromatography with fluorescence detection. Metabolic ratio of metoprolol/α-hydroxymetoprolol 3 hours post-dose was used for CYP2D6 phenotyping. Three allelic variants P450 2D6 *3, *4 and *6 were analysed.

Results: We observed a significant correlation (r_s = 0.8418, P = 0.0003) between the metoprolol/α-hydroxymetoprolol MR after metoprolol first ingestion and in steady state. All the patients were phenotyped as extensive metabolizers in both periods, despite statistically significant differences between the median MRs (0.59 versus 0.81, P = 0.0266).

Significantly higher normalized metoprolol serum concentrations, normalized metoprolol AUC_{0-4} and lower metoprolol oral clearance was observed in patients with

lower CYP2D6 metabolic activity. A trend towards lower resting heart rate before metoprolol intake was also observed in this group of patients. The differences in metoprolol disposition were more expressed when CYP2D6 phenotype instead of genotype was determined. Discordance between CYP2D6 genotype and phenotype was observed. Three patients were phenotyped as poor metabolizers compared to one when genotyped.

In the case report we described a 66-year-old polymorbid female patient on long-term treatment with metoprolol. She was repeatedly complaining about increased tiredness and dyspnoea on exertion. Phenotyping revealed a poor metabolizer with metabolic ratio of metoprolol/α-hydroxymetoprolol 104.3, genotyping revealed an intermediate metabolizer CYP2D6*4/*9. Metoprolol dose was reduced to half (100mg daily) the patient´s condition improved. After propafenone discontinuation the metabolic ratio metoprolol/α-hydroxymetoprolol dropped to 1.4 indicative of a phenotypic shift.

Conclusions: Metoprolol/α-hydroxymetoprolol MR in steady state is an appropriate alternative to metoprolol/α-hydroxymetoprolol MR after a single dose.

Significant variations exist in metoprolol disposition in hypertensive patients. Both genotyping and phenotyping provides a valuable method in determining enzymatic activity and in optimising metoprolol therapy.

Co-administration of propafenone to metoprolol may result in elevation of metoprolol serum concentration even with impact on patient´s clinical condition. Therapeutic drug monitoring could serve as a valuable tool in clarifying patient´s condition.