Oral

[O26-4] O26-4: Pharmacogenomics (2)

Chairs: Tsuyoshi Fukuda, USA / Taisei Mushiroda, Japan
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[O26-4-3] Genetic polymorphisms of CYP2B6, CYP2C19, CYP2D6 and CYP3A4 genes and methadone therapy

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Background

Methadone is metabolized by several polymorphic enzymes. Given as racemate, stereo-specificity of its metabolism can further compound the complexity and this can impact therapy for opiate dependence.

Methods

Patients on MMT program at selected incarcerated centers and methadone clinics in Malaysia were examined for polymorphisms at *CYP2B6*, *CYP2C19*, *CYP2D6* and *CYP3A4* loci. Serum concentrations of *(R)*-, *(S)*-methadone and methadone metabolite (EDDP-2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) were also measured.

Results

The 187 patients enrolled were divided into groups to reflect compliance status. The first group comprised patients from incarcerated settings given directly observed doses. The second group comprised patients from ambulatory methadone clinics. Average dose in Group I patients was higher compared to Group II patients (78.9mg *vs* 57.5mg; p=0.000). Although Group II patients had higher serum drug concentrations, the differences did not reach statistical significance. Among Group I patients, carriers of the **6/*6* and **4/*4* genotypes showed a 2.2-fold higher *(S)*-methadone and a 1.4-fold higher *(R)*-methadone serum concentrations compared to non-carriers of **6* and **4* (P = 0.022). However, *(R)*-methadone concentrations were not significantly different among the 3 genotype groups although there was a trend towards higher concentrations with carriers of homozygous **4* and **6*. *CYP2D6, CYP3A4* and *CYP2C19* genotypes did not influence *(R)*-, *(S)*-, or *(R,S)*-methadone serum concentrations

Conclusions

Patient’ s non-compliance altered the relationship between daily methadone doses and serum drug concentrations. It must be accounted for in assessing pharmacogenetic influence on MMT. Of the genes studied, only CYP2B6 appeared to influence methadone metabolism. Preferential metabolism of active S-methadone is an important consideration for methadone in pharmacogenetically diverse populations of opiate users especially when it is administered as a racemate mixture.