K22 Can Pharmacogenetic Studies Improve the Effectiveness of Methadone Maintenance Programs?

Shu-Ching Yang, MS, and Shiao-ping Huang, PhD, Department of Medical Laboratory Sciences and Biotechnology, Fooyin University, Kaohsiung Hsien, Taiwan; Ming-Yu Yang, PhD, Graduate Institute of Clinical Medical Sciences, Chang Gung University, Kaohsiung, Taiwan; Ray H. Liu, PhD, Department of Medical Laboratory Sciences and Biotechnology, Fooyin University, Kaohsiung Hsien, Taiwan; Shang-Jang Wang, MS, Department of Laboratory Medicine, Kaohsiung Kai-Suan Psychiatric Hospital, Kaohsiung, Taiwan; Hung-Chi Wu, MS, Department of Addiction Prevention and Treatment, Kaohsiung Kai-Suan Psychiatric Hospital, Kaohsiung, Taiwan; Yeou-Lih Huang, PhD, Department of Medical Laboratory Science and Biotechnology, Kaohsiung Medical University Kaohsiung, Taiwan; and Jih-Heng Li, PhD, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*

After attending this presentation, attendees will better understand how the effectiveness of methadone maintenance program can be improved by pharmocogenetic studies.

This presentation will impact the forensic science community by explaining how the utilization of modern technologies, including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and single nucleotide polymorphism (SNP) for studying genetic variants and gas chromatography-mass spectrometry (GC-MS) analysis of pharmacokinetic parameters, would help place the maintenance program on a higher scientific ground.

Following the implementation of the "harm reduction" policy, methadone (MTD) has now been widely adopted for "treating" heroin addicts in Taiwan. In humans, MTD is metabolized by *N*-demethylation to 2-ethylidene-1,5-di-methyl-3,3-diphenyl-pyrrolidine (EDDP) and 2- ethyl-5-methyl-3,3-diphenyl- 1-pyrrolidine (EMDP). It has been reported that: (a) treatment effectiveness was highly affected by the prescribed dose; and (b) patients receiving the same dose responded differently. With this understanding, a study was conducted on pharmacogenetic parameters of patients in a local MTD maintenance program, focusing on understanding the relationships between patients' plasma level of MTD (and its metabolites) and their treatment dose and genetic polymorphisms of ABCB1 and CYP2C19. Gas chromatography-mass spectrometry was used for the determination of these analytes' concentrations in plasma, while polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and single nucleotide polymorphism (SNP) genotyping assay were used for the analysis of genetic variants. The concentration of MTD, EDDP, and EMDP found in 55 patients (prescribed dose = 10-165 mg/day) were 39.2-805 ng/ml, 1.18-127 ng/ml, and < 0.5-38.3 ng/ml, respectively. For the low-dose group (< 50 mg/day), correlations of MTD dosage and the observed plasma concentrations of MTD and EDDP were $R^2 = 0.638$ and $R^2 = 0.680$, respectively. For the high-dose group (≧ 50 mg/day), the corresponding correlations were $R^2 = 0.141$ and $R^2 = 0.103$. The latter finding suggests that the observed concentrations of MTD and EDDP

might be associated with these patients' pharmacogenetic characteristics. Findings derived from PCR-RFLP and SNP genotyping assays include:
(a) patients with GT, GA, TT, TA, and AA variants in their ABCB1 G2677T/A were associated with high EDDP plasma level ($p = 0.003$); (b) patients with 681A and 990T in CYP2C19 were associated with low EDDP plasma level ($p = 0.015$, 0.010, respectively); and (c) no definite pattern of plasma drug concentration could be established ($p > 0.05$) for patients with SNP C1236T and C3435T (in ABCB1) variants. In conclusion, understanding pharmacokinetic and pharmacogenetic parameters can potentially improve the effectiveness and safety in the implementation of the maintenance program.

Methadone Maintenance Program, EDDP, Pharmacogenetics

 ** Presenting Author*