

Pharmacogenetic Research in Psychiatry: The Relevance to Therapeutic Effects of Psychotropics in Schizophrenia, Mood Disorder and Panic Disorder

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The dosage of psychotropics is usually adjusted according to the clinical response to the drugs and also the administration of the drugs should be terminated or the drug should be changed when the patients have poor clinical response. Therapeutic drug monitoring data of the drugs are valuable when making such clinical decision. For example, the number of patients with schizophrenia who had a positive response to bromperidol or haloperidol did not increase after the plasma levels of such drugs reached 12 ng/mL. Plasma levels of tricyclic antidepressants (TCAs) such as clomipramine and amitriptyline varied considerably between individuals or different ethnics treated even with the same daily dose, which suggests interindividual and interethnic differences in drug metabolism which is partly due to genetic polymorphism of drug metabolizing enzyme such as CYP2D6 or CYP2C19. Analysis of the relationship between the concentrations of tertiary amine TCAs including their metabolites revealed that lower desmethylated capacity predicts good clinical response to TCAs. In Japan, fluvoxamine, the first selective serotonin reuptake inhibitor (SSRI), was introduced in clinical practice in May, 1999. In November 2000, paroxetine was launched as the second SSRI into Japanese market. Pharmacological intervention for psychiatric disorders including mood disorder, obsessive compulsive disorder and panic disorder has been shifted from TCAs to SSRI. The plasma levels of paroxetine also vary among individuals even if the same daily dose of the drug is administered. From our data, the initial clinical response to paroxetine (at 2 weeks after initiation of the drug treatment) in the patients with panic disorder is inversely related to the plasma levels of paroxetine. In the range of plasma levels of paroxetine >20 ng/ml, it is estimated that the reduction ratio in the Panic and Agoraphobia Score (PAS) $(= (\text{PAS score at baseline} - \text{PAS score at 2 week}) / \text{PAS score at baseline})$ is < 0.2 , which suggest the existence of upper threshold of the plasma levels of the drug and the search of the determinant for the plasma levels of the drug is essential for the treatment of panic disorder.

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Education

- 1973~1976 Okayama Asahi Senior High School
1977~1983 Shiga University of Medical Science, received M.D.
1983~1987 Shiga University of Medical Science, Graduate School, majoring in Psychiatry and CNS Information Control. Received Ph.D. in March in 1987 for a thesis entitled "Periodic exposure to mother is potent zeitgeber of rat pups' rhythm." (published in *Physiology & Behavior* 36: 723-730, 1986)

Occupation

- 1987~1990 Instructor, Department of Psychiatry, Shiga University of Medical Science
1988~1990 Visiting Scientist from Japanese Ministry of Education, Department of Psychiatry, Brain & Development Research Center (Laboratory of Professor A.J. Prange Jr.), University of North Carolina at Chapel Hill, North Carolina, USA.
1990~1993 Head of Psychiatry Service, Toyosato Hospital.
1990~1993 Clinical Assistant Professor of Psychiatry, Shiga University of Medical Science.
1994~1998 Instructor, Department of Psychiatry, Shiga University of Medical Science
1995~1996 Visiting Scientist from Japanese Society of Clinical Pharmacology, Department of Clinical Pharmacology, Huddinge University Hospital (Laboratory of Professor Leif Bertilsson), Karolinska Institute, Sweden
1998~2002 Assistant Professor, Department of Psychiatry, Shiga University of Medical Science
2002~2006 Associate Professor, Department of Psychiatry, Dokkyo Medical Uni.School of Med.
2006~present Professor, Department of Psychiatry, Dokkyo Medical University School of Medicine

Professional Societies

- The Japanese Society of Psychiatry and Neurology
Japanese Society of Biological Psychiatry
Japanese Society of Neuropsychopharmacology
Japanese Society of Clinical Psychoneuropharmacology (Councillor)
Japanese Society of Clinical Pharmacology (Councillor)
International Society of Chronobiology
Society for Research on Biological Rhythms
Pacific Rim Association for Clinical Pharmacogenetics (Councillor)
Japanese Society of Psycho-oncology (Councillor)

Major Scientific Interests

Clinical Psychiatry; Chronobiology; Behavioral Sciences; Endocrine Research in Affective Disorders; Pharmacogenetics of Psychotropic Drugs