New research advances in ethno-psychopharmacology: an Asian perspective

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Asians represent more than half the world's population but themselves consist of very diverse genetic, ethnic, cultural and linguistic groups. Understanding the role of ethnicity in an individual's response to psychotropic medications is of importance in treating psychiatric disorders among Asians. Recent research has supported the notion that Asians carry distinct genetic profiles that can influence both the pharmacokinetics and the pharmacodynamics of a given medication (Lin & Smith, 2000; Pi & Simpson, 2005). In this brief review, we summarise the research findings in the field, focusing on pharmacogenetic variations between Asians and other ethnic groups.

The ability of an individual to respond to a particular pharmacological compound is mainly determined by his or her genetic composition. Genetic variations influence the way in which the body handles drugs through absorption, distribution, metabolism and excretion. The enzyme aldehyde dehydrogenase (ALDH), which is involved in ethanol metabolism, is the best illustration (Agarwal & Goedde, 1990). Approximately 50% of East Asians have a deficient form of the enzyme, which results in accumulation of acetaldehyde and the 'flushing' response to alcohol consumption. This 'deficient' phenotype is inherited through a dominant mutation in the ALDH2*2 allele. The ALDH2*2 allelic mutation disrupts the function of an ALDH subunit polypeptide and reduces the enzyme's activity (Wall *et al*, 2001). Because the mutation is dominant negative, individuals with either one (heterozygote) or two (homozygote) ALDH 2*2 alleles are slower to oxidise acetaldehyde during alcohol metabolism, resulting in facial flushing, nausea, dizziness and tachycardia. These individuals drink less alcohol and have lower rates of alcohol dependence than do wild-type ALDH2*1 homozygotes. In addition, 85–90% of Chinese and other East Asians carry a functional polymorphism of the alcohol dehydrogenase (ADH2) gene, which leads to a greater capacity to convert alcohol into acetaldehyde than the gene form found in most Caucasians. This ADH2 polymorphism has been shown to have a protective effect against heavy alcohol drinking and alcoholism.

Genetic variations also affect drug distribution. The plasma level of alpha-1-acid glycoprotein, for example, a plasma protein that provides binding sites in blood for many psychotropic drugs, is significantly lower in Asian than in Caucasian populations (Zhou *et al*, 1990).

The cytochrome system

The cytochrome P450 (CYP) system is a group of enzymes of great interest to psychiatrists because they metabolise a large number of psychotropic medications. These enzymes show considerable genetic variation and their activities can be induced or inhibited by specific substrates. Extensive genetic polymorphism of CYP enzymes results in individuals with a wide range of enzymatic activities, classified as extensive metabolisers (EMs), poor metabolisers (PMs) or slow metabolisers (SMs). The proportions of EMs, PMs and SMs vary among different ethnic groups. For example, in relation to the CYP2D6 enzyme, 1–6% of Asians are PMs whereas 5–10% Caucasians are PMs. On the other hand, with the CYP2C19 enzyme, 15–25% of Asians are PMs while 2–10% of Caucasians have little or no activity.

Drug response

Genetic profiles of Asian people also determine the effects of a drug on its target, such as receptors, transporters or neurotransmitters, and molecules involved in signal transduction pathways. Genetic variations are found in genes that encode the biosynthesis and catabolism of neurotransmitters, such as tryptophan hydroxylase (TPH), tyrosine hydroxylase (TH), catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). COMT is an enzyme that catalyses biodegradation of catecholamines, including dopamine. A transition from guanine (G) to adenine (A) at codon 158 of the COMT gene results in the substitution of methionine for valine (Val158Met), which is linked to low COMT enzymatic activity. The COMT polymorphism is reportedly associated with neuropsychiatric disorders, including schizophrenia and Parkinson's disease. Approximately 80% of Chinese, Japanese and Korean people carry the valine genotype, with high enzymatic activity as the phenotype, whereas 50% of Caucasians carry the phenotype with low enzymatic activity (Glatt *et al*, 2003).

Another example is the serotonin transporter gene (SLC6A4) polymorphism. The serotonin transporter is a target for tricyclic antidepressants and selective serotonin reuptake inhibitor (SSRI) antidepressants. The promoter region of the serotonin transporter is polymorphic; a short promoter leads to a low level of gene expression while a long promoter increases gene transcription of the transporter. It has been reported (Gelernter *et al*, 1997) that approximately 80% of Japanese, 40% of European–American and 30% of African–American people have the short-form genotype. Theoretically, such a difference may lead to a differential response to SSRI antidepressant treatment. Such an effect has been demonstrated in a genetically manipulated mouse model. However, a study with a small sample size

https://doi.org/10.1192/S1749367600001909 Published online by Cambridge University Press

comparing the clinical response to sertraline of Chinese and Caucasian patients showed no significant association of SLC6A4 polymorphism with drug response (Ng *et al*, 2006). Future studies are essential to determine whether genetic variations between Asian and non-Asian ethnic groups are associated with effective drug responses and side-effects of psychotropic medications.

The issues related to the pharmacokinetics and pharmacodynamics of specific psychotropic medications in Asians have been extensively reviewed elsewhere (Lin & Smith, 2000; Pi & Gray, 2000). It has been generally accepted that Asian patients require lower doses of antipsychotic medications than do Caucasian patients. It was reported that the plasma levels of haloperidol were 52% higher in Chinese than in Caucasian patients treated with equal weight-adjusted doses of medication (Potkin *et al*, 1984). In a different study, Caucasian patients had lower serum haloperidol and prolactin levels than Asian patients did (Lin *et al*, 1988*b*).

It has also been shown that Asian people are more vulnerable to the development of extrapyramidal side-effects, such as dystonia and Parkinsonism, from treatment with typical antipsychotics (Pi & Simpson, 2000). The rates of tardive dyskinesia differed among ethnic subgroups in Asia, varying from 8% in Beijing, China, to over 20% in Japan. Interestingly, different rates of movement disorders among Chinese in-patients in different regions of China suggest that not only genetic factors but also environmental factors contribute to the variations.

Researchers believe that there is no significant difference in pharmacokinetics of lithium among ethnic groups. However, surveys and case report series suggested that Asian people might respond to lower doses of lithium than non-Asian people. Optimal therapeutic lithium levels of 0.71 mmol/l and 0.73 mmol/l were recommended for Asians with bipolar disorder (Yang *et al,* 1991). Similar studies were carried out for antidepressant treatment in Asian patients (Pi & Gray, 2000). In general, Asian patients had higher mean peak plasma levels and greater areas under the curve (AUCs) than Caucasian patients did with a number of antidepressant treatments, including desipramine, clomipramine and nortriptyline. The possibility of ethnic variations in response to SSRIs has not yet been systematically studied. Further research into the ethnic variations of SSRI pharmacokinetics and pharmacodynamics is needed.

Studies of the pharmacokinetics of diazepam have indicated that Asian people have a lower volume of distribution, and serum levels of diazepam and its metabolite, desmethyldiazepam, were higher than in Caucasian people. Similar pharmacokinetic differences between Asian and Caucasian patients were also observed with alprazolam (Lin *et al*, 1988*a*).

Conclusion

Our society has become more ethnically and culturally diverse. An understanding of cross-cultural perspectives in psychopharmacology has become essential for clinicians. Many questions regarding the cross-cultural aspects of psychotropic medications remain unanswered. Research in pharmacogenetics will continue to provide more information regarding the genetic factors that influence pharmacokinetic and pharmacodynamic characteristics in Asian groups and non-Asian groups.

References

Agarwal, D. P. & Goedde, H. P. (1990) *Alcohol Metabolism, Alcohol Intolerance and Alcoholism: Biochemical and Pharmacogenetic Approaches*. Springer.

Gelernter, J., Kranzler, H. & Cubells, J. F. (1997) Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Human Genetics*, **101**, 234–246.

Glatt, S. J., Faraone, S. V. & Tsuang, M. T. (2003) Association between a functional catechol-O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case–control and family-based studies. *American Journal of Psychiatry*, **160**, 469–476.

Lin, K. M. & Smith, M. W. (2000) Psychopharmacology in the context of culture and ethnicity. In *Ethnicity and Pharmacology* (Review of Psychiatry Series, Vol. 19) (ed. P. Ruiz), pp. 1–36. American Psychiatric Press.

Lin, K. M., Lau, J. K., Smith, M. W., *et al* (1988*a*) Comparison of alprazolam plasma levels and behavioral effects in normal Asian and Caucasian male volunteers. *Psychopharmacology (Berlin)*, **96**, 365–369.

Lin, K. M., Poland, R. E., Lau, J. K., *et al* (1988*b*) Haloperidol and prolactin concentrations in Asians and Caucasians. *Journal of Clinical Psychopharmacology*, **8**, 195–201.

Ng, C. H., Easteal, S., Tan, S., *et al* (2006) Serotonin transporter polymorphisms and clinical response to sertraline across ethnicities. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, **30**, 953–957.

Pi, E. H. & Gray, G. E. (2000) Ethnopharmacology for Asians. In *Ethnicity and Pharmacology* (Review of Psychiatry Series, Vol. 19) (ed. P. Ruiz), pp. 91–113. American Psychiatric Press.

Pi, E. H. & Simpson, G. M. (2000) Medication-induced movement disorders. In *Kaplan and Sadock's Comprehensive Textbook of Psychiatry* (7th edn) (eds B. J. Sadock & V. A. Sadock), pp. 2265–2271. Lippincott, Williams & Wilkins.

Pi, E. H. & Simpson, G. M. (2005) Cross-culture psychopharmacology: a current clinical perspective. *Journal of Psychiatric Services*, **56**, 31–33.

Potkin, S. G., Shen, Y., Pardes, H., *et al* (1984) Haloperidol concentrations elevated in Chinese patients. *Psychiatry Research*, **12**, 167–172.

Wall, T. L., Shea, S. H., Chan, K. K., *et al* (2001) A genetic association with the development of alcohol and other substance use behavior in Asian Americans. *Journal of Abnormal Psychology*, **110**, 173–178.

Yang, Y. Y., Yeh, E. K., Chang, S. S., *et al* (1991) Maintenance lithium levels could be lowered: based on Taiwanese and Danish studies. *Journal of the Formosan Medical Association*, **90**, 509–513.

Zhou, H. H., Adedoyin, A. & Wilkinson, G. R. (1990) Differences in plasma binding of drugs between Caucasians and Chinese subjects. *Clinical Pharmacology and Therapeutics*, **48**, 10–17.