Pharmacogenetics of CNS drugs

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In 1980 we published two papers of importance for the future of our research: (i) it was shown that the two polymorphic hydroxylations of debrisoquine and sparteine are catalysed by a common enzyme now called CYP2D6 and (ii) that this enzyme also catalysed the metabolism of the tricyclic antidepressant nortriptyline. Later it was shown that most antidepressants are metabolised by CYP2D6. (1) There are many allelic variants of *CYP2D6* causing decreased (e.g. *CYP2D6*10* in Asians) or no (*4 in Caucasians) activity o f the enzyme. We have identified duplication and amplification of a *CYP2D6* gene as a cause of ultrarapid metabolism. There are pronounced interethnic differences in these allelic variants. When nortriptyline was given as single doses to healthy subjects there was a close relationship between the rate of 10-hydroxylation and the number of functional *CYP2D6* genes (1).

Most neuroleptic drugs are also metabolised by CYP2D6. Exceptions are the atypical neuroleptics clozapine and olanzapine, which are mainly metabolised by CYP1A2. In several studies in both healthy subjects given single doses and in patients treated chronically a relationship between haloperidol disposition and CYP2D6 geno/phenotypes has been established (1). In Koreans this relationship was confirmed at doses of haloperidol below 20 mg per day, but not at higher doses (2). These and other studies taken together show that at low doses haloperidol is metabolised by CYP2D6, while at high doses this enzyme is saturated and then enzymes with a higher capacity e.g. CYP3A4 are more important.

CYP2D6 catalyzes the metabolism of at large number of psychotropic drugs and the pronounced variation in its activity between individuals and populations contributes to the variation in treatment response and side-effects. Also it must be emphasized that when two drugs, which both are substrates of CYP2D6, are co-administrated they may increase each others plasma concentrations and potentiate therapeutic effects and adverse drug reactions.

Another polymorphic enzyme CYP2C19 metabolizes several CNS drugs e.g. diazepam and

clomipramine. About 3 % in Europe and 15-20 % in Asia are poor metabolizers of the probe drugs mephenytoin and omeprazole. The higher incidence in Asia is due to the presence of the *CYP2C19*3* in addition to the *CYP2C19*2* allele, which is present at a similar frequency in both populations. A Japanese population of depressed patients had higher plasma concentrations of clomipramine than corresponding Swedish patients (3). This is most probably due to a decreased activity of CYP2C19, which catalyzes the demethylation of clomipramine.

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2. Roh HK, Chung JY, Oh DY, Park CS, Svensson JO, Dahl M-L, Bertilsson L. (2001) Br. J. Clin Pharmacol, 52:265-271
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