THE RELEVANCE OF ETHNIC INFLUENCES ON PHARMACOGENETICS TO THE TREATMENT OF PSYCHOSIS

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CONTENTS

SUMMARY

Interethnic variation amongst the drug metabolising enzymes relevant to the treatment of psychosis is reviewed. The frequency of genetically determined variants at the extremes of enzyme activity is seen to vary considerably between different ethnic groups; in addition, a shift in the frequency distribution giving an overall lower population mean activity may occur. The role of dietary and other environmental influences in the generation of interethnic variation in cytochrome activity is also discussed. Clinical studies pertinent to this variation are reviewed. It is suggested that the reason for conflicting data from some clinical studies is the existence of overlapping substrate specificity, so that one cytochrome is able to substitute for another. Individuals deficient for more than one cytochrome would be likely to show much more pronounced clinical effects than those showing single cytochrome deficiency.

KEY WORDS

ethnicity, pharmacogenetics, metabolism, cytochrome P450, antipsychotics

INTRODUCTION

The term pharmacogenetics was coined when adverse drug reactions were first attributed to genetic factors /1/. Genetic factors affect both drug metabolism (pharmacokinetics) and drug response at the level of the target organ (pharmacodynamics). With respect to interethnic variation affecting the treatment of psychosis, pharmacokinetic genetic factors, encoding the drug metabolising enzymes (or DMEs), have been far more extensively investigated than interethnic variation affecting pharmacodynamic genetic factors. This review will therefore focus mainly on the DMEs.

An important subset of the DMEs is the group of cytochrome P450 enzymes (CYPs), or haem-thiolate proteins. These enzymes metabolise not only drugs, but also endogenous compounds (*e.g.* steroids), plant products, and man-made environmental toxins. Three members of this family of enzymes have been described to be involved in the metabolism of antipsychotics: CYP2D6, CYP3A4, and CYP1A2.

Other enzymes in this family, including members of the CYP2C subfamily, should also be considered, especially with regard to drug-drug interactions.

1. CYP2D6

1.1 Genetic variation in CYP2D6

Four different levels of activity of CYP2D6 have been identified, through the use of probe drugs which are metabolised by the enzyme. An individual may be termed an ultrarapid metaboliser (UM), extensive metaboliser (EM), intermediate metaboliser (IM), or poor metaboliser (PM). This variation in enzymatic activity is due to multiple allelic variants of *CYP2D6* (the gene encoding the protein), the frequencies of which differ in different ethnic groups /2,3/.

In Caucasian populations, the frequency of PMs is 5-10% /4/, while in Black Africans the frequency is 0-8% /5-7/, in African-Americans the frequency is 3.7% /8/, and in Orientals (Chinese, Japanese, and Koreans having been studied) the frequency is approximately 1% /9-14/. In addition, a lower population mean enzyme activity has been observed in Chinese, Zimbabweans, and Ghanaians as compared to Caucasians. The low PM frequency in Orientals is caused mainly by the very low frequency of the *CYP2D6*4* mutant allele, an allele which is associated with absent enzyme activity and accounts for about 66% of PM alleles in Caucasians /3/. The lower population mean enzyme activity has been attributed to the relatively high frequency of *CYP2D6*10* in the Chinese, and of *CYP2D6*17* in the Ghanaians and Zimbabweans, both of which alleles being associated with diminished CYP2D6 activity /15-18/. The *CYP2D6*17* allele also occurs at a greater frequency in African-Americans /8/. Dahl *et al.* /19/ compared findings in a pilot study on Koreans, Chinese, and Japanese, and found that the frequency of *CYP2D6*10A* and *CYP2D6*10B* was somewhat lower among the Koreans than among the Chinese or Japanese. Therefore findings from one ethnic group may not be applicable to another geographically close and apparently similar ethnic group. Canadian Native Indians are descendants of North Asian populations, and have been found to resemble Chinese in terms of PM frequency, but to lack the shift towards a lower mean enzyme activity (Fig. 1) /20/. This was

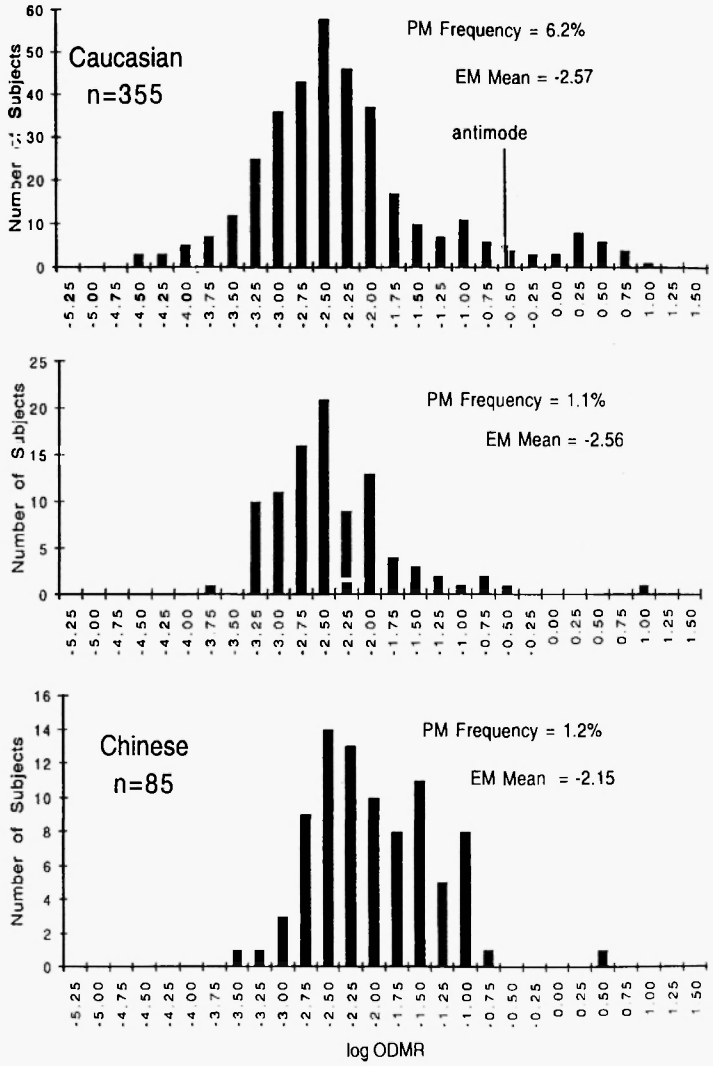

Fig. 1: Frequency distributions of dextromethorphan O-demethylation ratios in Caucasian, Canadian Native Indian (central graph, n=115), and Chinese populations. Dextromethorphan is metabolised by CYP2D6, and the O-demethylation ratio (ODMR) is a measure of CYP2D6 enzyme activity, where the higher the ratio, the lower the enzyme activity. (From: Nowak MP, Tyndale RF, Sellers EM. CYP2D6 phenotype and genotype in a Canadian Native Indian population. Pharmacogenetics 1997; 7: 147, with permission.)

seen to be due to a lower frequency of the *CYP2D6*3* and *CYP2D6*4* mutant alleles relative to Caucasians, and a lower frequency of *CYP2D6*10* compared with the Chinese. Similarly, a relatively low frequency of *CYP2D6*10* has been found in the South-Amerindian population of Chile /21/. This genetic drift has been interpreted as possibly due to a founder effect, mitochondrial DNA sequence variations revealing that these two groups of Amerindians were derived from a small number of maternal lineages /22/, or due to genetic selection pressures by dietary or other environmental factors. Middle Eastern populations show a very low frequency of CYP2D6 PMs, resembling Orientals rather than Caucasians in phenotyping studies (reviewed in /23/).

A further factor to be considered amongst individuals of lower CYP2D6 activity is that in Black African populations, individuals who appear to be PMs when tested with one drug may not be PMs when tested with another drug, the two drugs both being metabolised similarly by CYP2D6 in Caucasians /5,24-26/. This has been suggested to be due either to the presence of an as yet unidentified CYP2D6 variant with differential substrate specificity, or to inter-ethnic variations in conjugation and/or renal tubular transport.

At the other end of the spectrum of enzyme activity, the frequency of UMs also differs markedly between different ethnic groups, being 0.8-2% in Danes or Swedes /27,28/, 3.6% in Germans /29/, less than 5% in Black Zimbabweans /7,30/, 7% in Spaniards /31/, 20% in Saudi Arabians /32/, and 29% in Ethiopians /33/.

1.2 Clinical relevance

It has been suggested that PMs and IMs might show a tendency towards higher serum levels of drugs metabolised by CYP2D6 for a given dose, and might therefore be more susceptible to adverse effects (*i.e.* be treatment-intolerant), whereas UMs might show particularly low serum levels at standard doses and might therefore appear to be treatment-refractory. In accordance with this, in studies on normal volunteers, PMs were shown to have significantly higher serum levels of perphenazine /34/ and zuclophenthixol /35/, while the oral clearance of perphenazine and zuclopenthixol in patients on continuous treatment was shown to be significantly predicted by CYP2D6 genotype /36/.

CYP2D6 is also involved in the metabolism of haloperidol, fluphenazine, and trifluperidol /37/. Case reports support an association between PM status and a higher susceptibility to adverse effects /38,39/. A trend towards an excess of mutant *CYP2D6* alleles has been seen in schizophrenics with movement disorders /40/. However, another study has not found an excess of PMs amongst schizophrenics intolerant of typical antipsychotics (Aitchison *et al.*, unpublished data).

Haloperidol concentrations have been found to be elevated in Chinese patients suffering from schizophrenia /41/. Although this could also be due to interethnic variations in CYP3A4 activity (see below), it would be consistent with the lower mean CYP2D6 activity seen in Chinese. Nyberg *et al.* /42/ showed that a PM of CYP2D6 had higher concentrations of plasma haloperidol throughout a 4-week treatment period with haloperidol decanoate compared with 7 EMs of CYP2D6. Suzuki *et al.* /43/ studied 50 Japanese schizophrenic patients, and found a higher mean steady-state plasma haloperidol concentration in patients with one mutant allele (mainly *CYP2D6*10*) as compared with patients with no mutant alleles, and a higher mean steady-state plasma reduced haloperidol concentration in patients with 1 or 2 mutant alleles as compared with patients with no mutant alleles. However, Lin *et al.* /44/ found that on a fixed dose weight-adjusted regime, Oriental patients had only a slightly increased mean haloperidol plasma level. Nonetheless, they had a significantly higher rating for extra pyramidal symptoms (EPS), and also higher concentrations of prolactin in response to haloperidol /45/. This could be due to a pharmacodynamic interethnic difference, *e.g.* due to variability in the dopamine D_2 receptor, or to interethnic differences in CYP3A4 (see below).

With regard to UM status, two patients have been described for whom particularly high doses of tricyclic antidepressants metabolised by CYP2D6 were required in order to achieve a therapeutic response /46/. However, in a study comparing 73 patients who were treated with typical antipsychotics and found not to be treatment-refractory with 235 treatment-refractory patients, an excess of UMs was not found in the refractory group /47/. On the contrary, a trend towards an excess of UMs was found in the non-refractory group, although the numbers of UMs were very low in both groups (2 and 3 in the refractory and non-refractory groups, respectively). This argues against

ultrarapid hydroxylation by CYP2D6 of typical antipsychotics being a major cause of failure to respond to treatment with these agents.

Risperidone and sertindole are metabolised by CYP2D6 to 9-OH-risperidone and dehydrosertindole respectively. Although 9-OH-risperidone has antipsychotic activity, and the *combined* plasma concentrations of risperidone and this metabolite would be expected to be similar for individuals with different ends of the spectrum of CYP2D6 activity, it differs somewhat from risperidone in its *in vitro* receptor profiles and protein- and brain-binding characteristics /48/. The antipsychotic activity of dehydrosertindole appears to be less than sertindole, with the mean serum levels of sertindole being up to 3-fold higher in PMs than in EMs. However, trials to date do not show a clear relationship between sertindole concentrations and therapeutic effect, and sertindole has a significant alternative pathway via CYP3A4. *In vitro* work reported a role for CYP2D6 in clozapine metabolism /49/; however, no association has been found between CYP2D6 genotype and clozapine response /50/. This is consistent with later work that has shown that the predominant enzymes in clozapine metabolism are CYP1A2 and CYP3A4 /51/. Nonetheless, the inhibitory effect of the selective serotonin reuptake inhibitors (SSRIs) paroxetine, fluoxetine, and sertraline on clozapine metabolism may be partly accounted for by CYP2D6-mediated interactions /52/.

In summary, the clinical data regarding CYP2D6 metaboliser status and response are confusing. It is possible that in certain individuals, CYP2D6 plays a factor in either the generation of adverse effects or lack of therapeutic response, but that when studies are conducted on patient populations, other factors, such as the overlapping substrate specificities of CYP enzymes, or pharmacodynamic factors cloud the picture so that the results seen in case reports are not replicated in larger studies.

2. CYP3A4

2.1 Variability in CYP3A4 activity

CYP3A4 is present in the liver and small intestine, and plays a role in the metabolism of many typical antipsychotics, sertindole, and clozapine /48/. This enyzme can be induced, inhibited, or inactivated

by drugs as well as environmental factors including food substances. Interpopulation variation in activity may therefore arise not only secondary to intrinsic variation in enzyme activity, but also secondary to the effect of environmental agents.

Nifedipine is a cardiovascular drug that is metabolised by CYP3A4 and has been used as a probe drug to investigate CYP3A4 activity in different populations. It has been shown that South Asians (from the Indian subcontinent) oxidise nifedipine at a significantly slower rate than Caucasians (Fig. 2) /53,54/, resulting in sustained haemodynamic changes. In the first study by Ahsan and colleagues, the South Asians had retained their original dietary practices, whereas the Caucasians consumed a typical Western diet. The effect of diet was studied in six Caucasians by giving them an Indian diet for 3 days prior to the administration of nifedipine; no significant difference in any of the pharmacokinetic parameters was detected.

Similarly, the N-demethylation of codeine, which is catalysed by an enzyme of the CYP3A subfamily, occurs at a significantly slower rate in Chinese as compared to Caucasians /55/. Interestingly, Chinese have also been shown to have a significantly lower mean codeine N-demethylation activity as compared to Japanese /56/.

Recently an A→G point mutation has been found in the nifedipine specific element (NFSE) at position -289 in the 5′ flanking region of the CYP3A4 gene /57/. This mutation has been further analysed in 59 Taiwanese, 59 Finnish, and 75 African-American subjects, and found to show an allelic frequency of 0%, 4.2%, and 66.7% in these populations, respectively (Sata, personal communication). Functional studies have not yet been performed, but it could well be the case that this mutation is the primary mutation responsible for interethnic variations in CYP3A4 activity.

2.2 Clinical considerations for CYP3A4

Drugs and food substances may act on the CYP3A4 present in the small intestine as well as that present in the liver. Indeed, the effect of a given agent on the two CYP3A4s may differ. For example, consumption of some furanocourmarins present in grapefruit juice can cause inactivation of enterocyte CYP3A4 while having no detectable effect on liver CYP3A4 activity /58/. Conversely, some oral drug regimens have been shown to increase liver CYP3A4 activity while having no effect on small bowel CYP3A4. It appears that some drugs

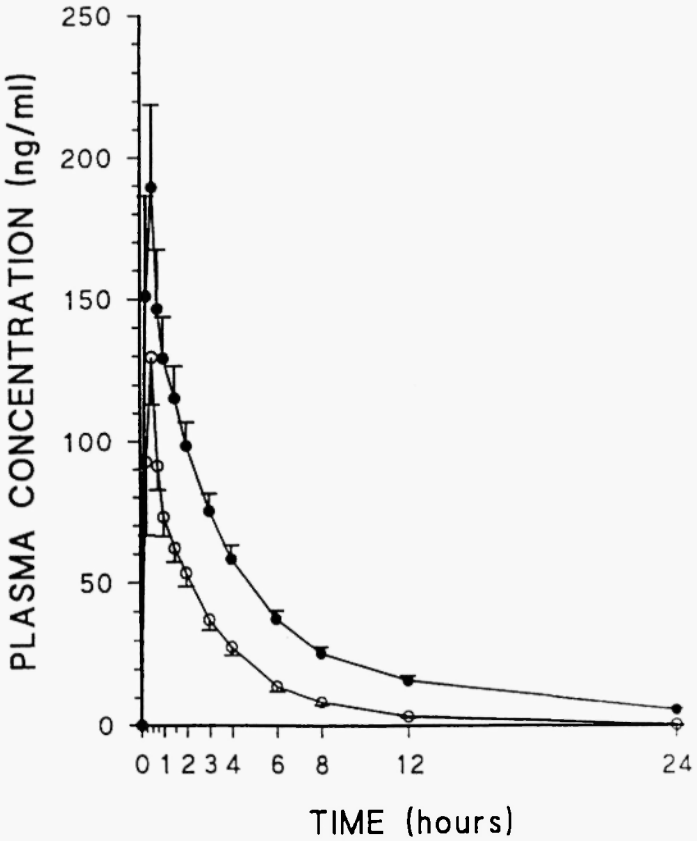

Fig. 2: Plasma concentration-time curves for nifedipine after 20 mg capsules were administered to Caucasian subjects (open circles; n=27) and South Asians (solid circles; n=30). Data are mean values with standard errors shown as vertical bars. (From: Ahsan CH, Renwick AG, Waller DG, Challenor VF, George CF, Amanullah M. The influences of dose and ethnic origins on the pharmacokinetics of nifedipine. Clin Pharmacol Ther 1993; 54: 333, with permission.)

(including benzodiazepines) undergo substantial first pass metabolism by enterocyte CYP3A (CYP3A4 and sometimes CYP3A5).

Recent work has shown that CYP3A4 is the responsible for the back oxidation of reduced-haloperidol to haloperidol and also for the N-dealkylation of haloperidol /59,60/. A negative correlation between clinical response and reduced-haloperidol levels or reduced-halo-

peridol/haloperidol ratios has been observed /61/; hence individuals with higher CYP3A4 activity could respond better to haloperidol than those with lower CYP3A4 activity. In a study on newly hospitalised Chinese patients with schizophrenia, Lane and colleagues found that those who experienced EPS had significantly higher reduced haloperidol concentrations and reduced-haloperidol/haloperidol ratios than the other patients /62/. A trend towards higher haloperidol concentrations was also found in the EPS group. This would be consistent with individuals with lower CYP3A4 activity being more vulnerable to EPS.

CYP3A4 is readily induced by carbamazepine; for most typical antipsychotics twice as much antipsychotic is required to achieve the same plasma concentration in the presence of carbamazepine as in the absence of carbamazepine /48/. This interaction is relevant for the treatment of schizoaffective psychoses. Other substances inhibit metabolism by the CYP3A enzymes (Table 1, modified from /63/). Clozapine toxicity has been reported after the coadministration of erythromycin /64/. Individuals who are CYP2D6 poor metabolisers or who are in receipt of drugs that inhibit CYP2D6 metabolism would be expected to be at increased risk of effects secondary to drug interactions at CYP3A4, and *vice versa*.

TABLE 1

CYP3A inhibitors (modified from /63/)

SSRIs (fluoxetine, fluvoxamine), SNRIs (venlaflaxine, nefazodone)
Steroids (oral contraceptives, prednisolone, tamoxifen, etc.)
Antibiotics (erythromycin, troleandomycin, clarithromycin, isoniazid)
Antifungals (ketoconazole, itraconazole)
AntiHIV drugs (ritanovir, zidovudine)
Analgesics (e.g. dextropropoxyphene)
Anaesthetics (e.g. lidocaine)
Cardiac drugs (nifedipine, verapamil)
Immunosuppressants (cyclosporin)
Cimetidine

3. CYP1A2

3.1 Variation in CYP1A2 activity

CYP1A2 is involved in the metabolism of many typical antipsychotics, clozapine, and olanzapine. A preliminary study showed evidence of interethnic variation, with Japanese showing an increased maximum plasma concentration of olanzapine after a given dose, and a mean half-life of 34 hours as compared with 24 hours in Caucasians /48/. Le Marchand *et al.* /65/ also showed significantly lower CYP1A2 activity in a group of 45 Japanese as compared with 15 Caucasians living in Hawaii. Nakajima *et al.* /66/ showed that CYP1A2 activity as measured by caffeine 3-demethylation was bimodally distributed in a group of 205 Japanese, with 14.1% being poor metabolisers. Other groups have also shown a multimodal distribution of CYP1A2 activity in most /67-70/, but not all /67,69/ populations. Relling *et al.* /71/ showed that CYP1A2 activity was significantly lower in a group of 63 Black subjects as compared with a group of 246 White subjects ($p = 0.036$).

This enzyme is also involved in the metabolism of aromatic and heterocyclic amines, and in most populations is found to be induced by smoking /66-70, 77/. The effect of smoking appears to be absent in Chinese /68/, which has been proposed to be secondary to the lower level of smoking in this ethnic group. Oral contraceptives, postmenopausal replacement oestrogens, and pregnancy appear to reduce CYP1A2 activity /65,73,74/. The lower CYP1A2 activity in women as compared to men appears to be explained by the effect of oestrogens /65/. Le Marchand and colleagues /65/ also found that lutein (which is found in green leafy vegetables) inhibits CYP1A2 activity. Caffeine and paracetamol (acetaminophen) intake increases CYP1A2 activity, as does the consumption of cruciferous vegetables (cabbage, broccoli, Brussels sprouts and watercress). However, the amount of cruciferous vegetable (*e.g.* 500 g broccoli daily for 10 days) required to increase CYP1A2 activity is considerably higher than that commonly present in a normal diet. Intake of meat cooked rapidly at a high temperature has also been shown to increase CYP1A2 activity /75/.

Although environmental factors such as the above are important in contributing towards variability in CYP1A2 activity, Le Marchand and colleagues /65/ found that 73% of the variability remained unexplained after taking into account the major environmental contributors to

the variance in 90 subjects of various ethnic backgrounds in Hawaii. A significant contributor to the variance may be genetic in origin, as suggested by work with inbred mice /76/. A mutation in the promotor region of CYP1A2 has recently been found (Aitchison *et al.*, unpublished data). This mutation shows significant interethnic variation: the frequencies of individuals heterozygous and homozygous for the mutation was found to be 2.3% and 1.1% respectively in 176 Caucasians and 24.4% and 4.1% respectively in 123 Taiwanese.

3.2 Clinical relevance of variations in CYP1A2 activity

The metabolism of clozapine *in vivo* appears to correlate with CYP1A2 activity, although CYP3A4, CYP2C19, and CYP2D6 are also involved /77,78/. Levels of clozapine of at least 350 to 420 ng/ml are associated with therapeutic response /79/, while the incidence of seizures and EEG abnormalities also appears to increase with dose. Elevated plasma clozapine concentrations in Chinese patients have been described (mean steady-state plasma clozapine concentration 60-100% higher than that found in Caucasians, /80/). At the opposite end of the spectrum, very low plasma clozapine levels despite high doses and compliance have been described, in association with very high CYP1A2 activity /81/. It is therefore possible that, analogous to the situation with CYP2D6, there exist individuals with ultrarapid CYP1A2 metaboliser status.

The most important pathways for olanzapine metabolism are CYP1A2, flavin-containing monoxygenase 3, and N-glucuronidation, with minor pathways including CYP2D6 and CYP2C19 /48/. Olanzapine clearance is increased in males (by about 30%) and in smokers, and decreased in the elderly, all of which are consistent with the involvement of CYP1A2. Evidence for the contribution of CYP1A2 to the pharmacokinetics of typical antipsychotics includes the effect of smoking: smoking increases the clearance of fluphenazine and haloperidol by 100% and at least 50% respectively in an affected population.

4. CYP2C ENZYMES

4.1 CYP2C genetics

Four members of the human CYP2C subfamily have been identified: CYP2C8, CYP2C9, CYP2C18, and CYP2C19 /82/; their genes form a cluster at chromosome 10q24. Of these, the role of CYP2C19 in the metabolism of psychotropic drugs has been most extensively studied. Relevant substances include amitriptyline, imipramine, clomipramine, moclobemide, citalopram, diazepam and desmethyldiazepam /83/, as well as clozapine, olanzapine, propranolol, and phenytoin to lesser extents. Four SSRIs (fluoexetine, sertraline, paroxetine, and citalopram) are all able to inhibit CYP2C19 and may also be metabolised by this enzyme. *CYP2C18* lies distal to *CYP2C19* on chromosome 10, is 85.7% homologous to *CYP2C19*, and shows similar substrate specificity towards diazepam /84/, phenytoin /85,86/, and omeprazole /87/. Furthermore, Mamiya *et al.* /88/ found cosegregation of poor metaboliser mutations of CYP2C19 and CYP2C18, indicating that CYP2C18 may not be able to take over from CYP2C19 in individuals deficient in CYP2C19. CYP2C9 was shown by Hashimoto and colleagues /89/ to play a greater role than CYP2C19 in the metabolism of phenytoin, and the Leu^{359} allele, which is present in the heterozygous state in 3.4% of Han Chinese subjects /90/, was seen to be associated with a 40% reduction in the V_{max} for phenytoin.

The incidence of poor metabolisers (PMs) of CYP2C19 in different populations has been reviewed /23,91-93/. There is substantial interethnic variation: the frequency of PMs is 2-5% in Caucasians, 2% in Saudi Arabians, 4% in Black Zimbabweans, 5% in Ethiopians, 13% in Koreans, 15-17% in Chinese, 21% in Indians, and 18-23% in Japanese. Indeed, when the square root of the PM frequency (representing the total frequency of mutant *CYP2C19* alleles) was plotted versus longitude, an increase in this value versus longitude was seen, with a step in the value occurring somewhere between Saudi Arabia and Bombay (Fig. 3).

There are two wild-type *CYP2C19* alleles (*CYP2C19*1A* and *CYP2C19*1B*), and seven defective alleles which are responsible for the PM phenotype /93/. The most common defective allele is *CYP2C19*2A* (a $G_{681}A$ substitution in exon 5, which creates an aberrant splice site, previous name for this allele, *m1*). A variant of this allele, *CYP2C19*2B*, contains a $G_{276}C$ substition in exon 2 which creates a

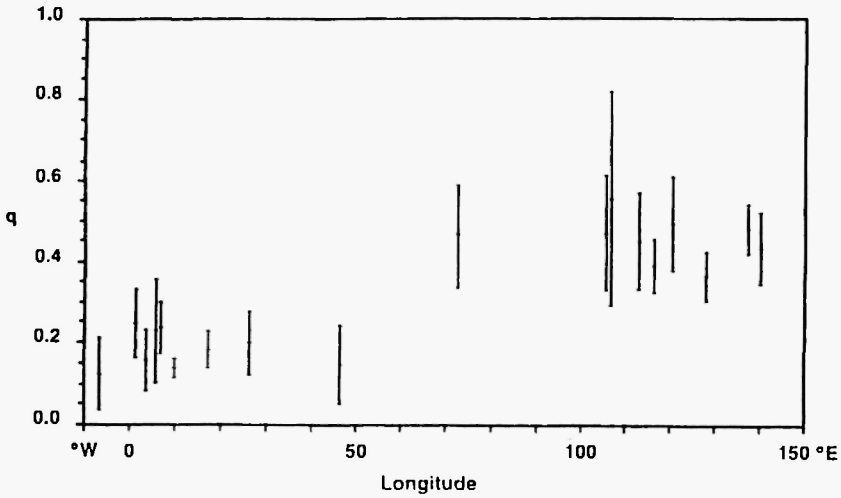

Fig. 3: Estimates of q, the total frequency of mutant CYP2C19 alleles, with 95% confidence limits in relation to longitude. (From: Price Evans DAP, Krahn P, Narayanan N. The mephenytoin (cytochrome P450 2C19) and dextromethorphan (cytchrome P450 2D6) polymorphisms in Saudi Arabians and Filipinos. Pharmacogenetics 1995; 5: 70, with permission.)

$Glu_{92}Asp$ change; this allele comprises 15% of the *CYP2C19*2* allele in Caucasians, but was not observed in 53 Japanese *CYP2C19*2* alleles studied. The two CYP2C19*2 alleles account for 86% of PM alleles in Caucasians and 69-87% in Orientals. The second major defective allele is *CYP2C19*3* (a $G_{636}A$ mutation in exon 4, which creates a premature stop codon, previous name for this allele, *m2*); this comprises 13-31% of PM alleles in Oriental populations and 1.5% in Caucasians. A third PM allele, *CYP2C19*4* (an A→G mutation in the initiation codon), accounts for 3% of Caucasian PM alleles. *CYP2C19*5* (a $C_{1297}T$ mutation in exon 9 which results in an $Arg_{433}Trp$ change in the haem binding region) accounts for 1.5% of Caucasian PM alleles and is rare in Orientals. *CYP2C19*6* (a $G_{395}A$ base substitution resulting in an $Arg_{132}Gln$ coding change in exon 3) and *CYP2C19*7* (a GT→GA mutation in the donor splice site of intron 5) each account for a further 1.5% of Caucasian PM alleles. *CYP2C19*8* (a $T_{358}C$ substitution resulting in a $Trp_{120}Arg$ change in exon 3) is a newly characterised, rare defective allele. The products of *CYP2C19*6* and *CYP2C19*8* show reduced catalytic activity (2% and 9%

of wild-type S-mephenytoin hydroxylase activity, respectively); the other mutants are associated with failure to express active CYP2C19. *CYP2C19*2A* and *CYP2C19*3* have both been identified in an Ethiopian population, and found to account for all the PM alleles in the 114 individuals studied /92/.

4.2 Clinical studies of CYP2C19

Omeprazole has been used as a probe drug in studies of CYP2C19 activity. In single-dose studies the clearance of omeprazole has been found to be higher in CYP2C19 EMs than PMs in Caucasians, Chinese, and Koreans, with the clearance in Caucasian EMs being significantly higher than that in both Chinese and Korean EMs /91/. After multiple doses of omeprazole, the mean areas under the plasma concentration-time curve for the parent drug indicated that heterozygous individuals had a reduced rate of metabolism as compared to homozygous EMs. It has therefore been hypothesised that the difference in clearance between Caucasians and Orientals is due to the relatively high proportion of heterozygous EMs among Orientals as compared with Caucasians.

In the case of diazepam, the clearance is significantly lower in Caucasian and Korean CYP2C19 PMs than EMs /91/. However, in Chinese, no significant difference between the elimination half-life of eight EMs and eight PMs was found, and the mean clearance in the whole group was relatively low as compared to Caucasians. It has been suggested that among the eight Chinese EMs, seven with a relatively low diazepam clearance might be heterozygous, which would explain the low overall clearance and the lack of significant difference between the EM and PM groups. Alternatively, differences in the contribution of CYP3A4 to diazepam pharmacokinetics in the different ethnic groups could explain the different findings. Like CYP2D6, CYP2C19 often functions as a high-affinity, low capacity enzyme, which is more important at low drug doses. With higher doses, multiple-dosing, or in the case of CYP2C19 deficiency, CYP3A4, which has a relatively high capacity and often shows relatively low substrate affinity, increases in its contribution to overall drug clearance. Schmider *et al* /94/ have calculated that even with single doses, approximately 60% of diazepam clearance is CYP3A4-dependent. The relatively high incidence of low CYP3A4 activity in Chinese may therefore contribute to the low mean diazepam clearance,

and, if polymorphisms in CYP3A4 and CYP2C19 do not cosegregate, could contribute towards the lack of a significant difference between diazepam clearance in S-mephenytoin PMs and EMs. It has been noted that "many Hong Kong physicians routinely prescribe smaller diazepam doses for Chinese than for white Caucasians" /95/; this tradition is consistent with the lower clearance found experimentally.

5. DRUG-DRUG INTERACTIONS

When prescribing psychotropic drugs that are subject to interethnic variations in metabolism, it is important to remember that interactions with non-psychotropic drugs at these sites may occur. A summary of substrates metabolised by the enzymes discussed above is listed in Table 2. Many enzymes show overlapping substrate specificity, and only the major routes of metabolism are shown. It should also be remembered that substances may exert considerable inhibitory effect at a given route, without being metabolised by that enzyme (*e.g.* quinidine in the case of CYP2D6). An individual who is a PM of a particular CYP enzyme will tend to be more susceptible to drug-drug interactions at the other cytochromes.

6. CONCLUSIONS

There is considerable interethnic variability in the activity of the DMEs. Although some studies aiming to show correlations between the activity of a single DME and clinical effects have yielded conflicting results, this may be because of the existence of alternative metabolic pathways using other DMEs. For example, in the case of CYP2D6 or CYP2C19 deficiency, CYP3A4 will often be able to play a substitutive role. Individuals who have a relatively low CYP2D6 or CYP2C19 activity will therefore be more susceptible to the effects of CYP3A4 inhibitors. Furthermore, it would be logical to hypothesise that while the clinical effects of single enzyme deficiency might not be consistent, the effects of deficiency of more than one enzyme might well be significant. This hypothesis is supported by the analagous finding of Rojas and colleagues /97/ that smokers with combined CYP1A1 and glutathione S-transferase M1 (GSTM1) deficiency showed significantly higher levels of activated DNA-bound potentially

TABLE 2

Some substrates of polymorphic CYP enzymes /83,94,96/

CYP2D6		CYP3A4			CYP1A2	CYP2C19	CYP2C9
Haloperidol	Codeine	Haloperidol	Carbamazepine	Progesterone	Chlorpromazine	Clozapine	Amitriptyline
Perphenazine	Dextromethorphan	Clozapine	Valproate	Oral	Trifluoperazine	Olanzapine	Zopiclone
Zuclopenthixol	Methadone	Sertindole	Codeine	contraceptives	Clozapine	Amitriptyline	Theophylline
Thioridazine	Methamphetamine	Amitriptyline	Dextromethorphan	Cortisol	Olanzapine	Imipramine	Phenytoin
Risperidone	Methylenedioxymeth-	Imipramine	Dextropropoxyphene	Prednisolone	Amitriptyline	Clomipramine	Tolbutamide
Sertindole	amphetamine*	Clomipramine	Orphenadrine	Amiodarone	Imipramine	Moclobemide	Warfarin
Amitriptyline	Propranolol	Fluoxetine	Erythromycin	Diltiazem	Clomipramine	Citalopram	
Clomipramine	Metoprolol	Fluvoxamine	Clarithromycin	Nifedipine	Zopiclone	Diazepam	
Imipramine	Pindolol	Sertraline	Doxycycline	Nimodipine	Tacrine	Propranolol	
Desipramine	Timolol	Nefazodone	Isoniazid	Nicardipine	Caffeine	Phenytoin	
Nortriptyline	Flecainide	Trazodone	Rifampicin	Digitoxin	Theophylline	Ibuprofen	
Fluvoxamine	Mexiletine	Venlafaxine	Trimethoprim	Proguanil	Aminophylline	Diclofenac	
Paroxetine	Perhexiline	Diazepam	Testosterone	Quinidine	Paracetamol	Naproxen	
Mianserin	Propafenone	Midazolam	Androstenedione	Cisapride	(Acetaminophen)	Omeprazole	
Desmethyl-	Metoclopramide	Clonazepam	Dapsone	Lidocaine	Zopiclone	Pantoprazole	
citalopram	Orphenadrine	Alprazolam	Dehydroepiandro-	Terfenadine		Proguanil	
Maprotiline	Ondansetron	Zolpidem	sterdione	Cyclosporin		Piroxicam	
Venlaflaxine		Caffeine	Oestradiol	Ondansetron			
		Theophylline	Tamoxifen	Vinblastine			

*also known as "ecstasy"

carcinogenic metabolites than individuals with CYP1A1 or GSTM1 deficiency alone. We have noted that there is a lower population mean CYP2D6 activity, lower CYP1A2 activity, and higher incidence of CYP2C19 poor metabolisers in Japanese as compared to Caucasians. Similarly, a lower population mean CYP2D6 activity and a much higher incidence of a mutation in the promotor of CYP3A4 has been found in Black subjects, while impaired CYP3A4 activity and a high frequency of CYP2C19 poor metabolisers has been found in individuals from the Indian subcontinent. We would therefore suggest that future studies focussing on the relevance of ethnic influences in pharmacogenetics to the treatment of psychosis should encompass methodology that is capable of analysing the variation in activity of all the DMEs (including the role of dietary and other environmental factors such as smoking) relevant to the population being studied. There is a paucity of studies addressing ethnic variation in pharmacodynamic factors; this issue should also be addressed in future work.

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