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Ethnic Differences in Drug Disposition and Responsiveness

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Summary

Interethnic differences are important factors accounting for interindividual variations in drug responsiveness. However, these differences in drug response have been a relatively neglected area of investigation, so that similar doses are prescribed to different ethnic populations without consideration of interethnic pharmacokinetic and pharmacodynamic variation. With the increased recognition of genetically determined polymorphism in metabolising ability as an important factor in drug disposition, concern has developed for the importance of individualising drug dose to account for racial differences. The recognition of these differences in drug disposition and responses calls into question the failure of drug licensing authorities to demand information on dosage, efficacy and toxicity in different ethnic groups, and to accept data from limited ethnic groups such as Caucasians.

This article reviews the evidence for ethnic differences in drug disposition and sensitivity and

should encourage further investigations to elucidate the extent of such differences, their causes and their therapeutic impact.

Early studies of new pharmacological entities are frequently carried out in a small number of individuals in Western Europe or North America. The information gained from these early studies is used to determine the appropriate drug dose, which is then applied to other populations of diverse ethnic backgrounds, often with minimal information on the potential differences that might exist in both drug disposition and sensitivity.

The purpose of this review is to examine the evidence for ethnic differences in drug disposition and sensitivity. Altered sensitivity may be first identified because of an abnormal response in one population compared with another when both populations receive similar drug doses. However, before designating such differences as being truly due to altered sensitivity it is important to exclude a pharmacokinetic cause resulting in altered drug concentrations. Such pharmacokinetic differences in populations may be environmental or genetic in origin; genetic differences may be monogenic or polygenic. In the absence of a pharmacokinetic explanation, true pharmacodynamic variability may occur when ethnic groups differ in their response to similar plasma drug concentrations.

1. Ethnic Variability in Polymorphic Traits of Drug Metabolism

1.1 Acetylation Polymorphism

Polymorphism of acetylation has been well known for over 30 years, since the discovery of isoniazid-induced nerve damage in slow acetylators (Hughes et al. 1954). Populations can be divided into slow and fast acetylators, with an individual's characteristic being determined by a single gene. Family studies have shown that slow acetylation is an autosomal, homozygous, recessive trait while rapid acetylators are either heterozygous or homozygous dominant (Evans et al. 1960). Some nongenetic factors including alcohol loading (Olsen & Morland 1978), glucose loading (Thom et al. 1981), steroid treatment (Raghupati Sarma et al. 1980), renal failure (Gold et al. 1976) and hepatic disease (Levi et al. 1968) are able to enhance or reduce acetylation. However, the effects of nongenetic factors are quantitatively less than those produced by genetic factors.

The substantial differences between slow and fast acetylators in their acetylation capacity can result in large disparities between the concentrations of both parent drug and metabolite in the 2 phenotypes. These differences in drug concentration alter the intensity of effect produced by acetylated drugs in the 2 populations. Slow acetylators have higher concentrations of drugs metabolised by acetylation such as isoniazid, hydralazine, procainamide, dapsone, sulphonamides, caffeine, nitrazepam and sulfasalazine (Weber & Hein 1985), and these elevated concentrations may result in increased pharmacological effect and drug toxicity. The development of antinuclear antibodies during hydralazine therapy occurs more frequently in slow acetylators, and blood pressure reduction is also greater in this group (Perry et al. 1970). Of additional interest, however, is that although Blacks who are slow acetylators appear to develop positive antinuclear antibodies at about the same rate, they seem less likely to develop systemic lupus erythematosus than Caucasians (Perry et al. 1970). Slow acetylators also appear to develop positive antinuclear antibodies and become symptomatic from lupus earlier in their treatment with procainamide (Henningsen et al. 1975; Woosley et al. 1978).

There are considerable interethnic differences in the frequency of the slow and fast acetylators (table I). Failure to take account of these differences can result in both therapeutic failures and (perhaps) unexpected toxicity.

Using isoniazid for the treatment of tuberculosis is complicated by the development of peri-

Table I. Frequency of slow acetylators in some populations

Population	No.	Frequency (%)	Reference
Black			
Sudan	102	65	Evans (1962)
Nigeria	109	49	Fawcett & Gammon (1975)
East Africa	204	55	Ellard & Gammon (1975)
US	242	42-51	Dufour et al. (1964); Harris (1961); Mitchell et al. (1960)
Caucasian			
Britain	472	55-62	Evans (1969); Philip et al. (1987)
Germany	524	57	Schmeidel (1962)
Canada	102	59	Eidus et al. (1974)
US	481	52-58	Evans et al. (1960); Mitchell et al. (1960); Dufour et al. (1964)
Chinese			
Taiwan	127	22	Sunahara et al. (1963)
Britain	59	22	Evans (1963)
Singapore	386	22	Ellard et al. (1977)
Hong Kong	184	22	Ellard et al. (1977)
Thailand	47	34	Kukongviriyapan et al. (1984)
Mainland of China	108	13	Horai et al. (1988)
Eskimo			
Canada	328	5-6	Armstrong & Peart (1960); Eidus et al. (1974)
Alaska	157	21	Scott et al. (1969)
Japanese			
Japan	1990	7-12	Sunahara et al. (1961); Horai & Ishizaki (1988)
US	209	10	Dufour et al. (1964)

pheral neuropathy, which appears to occur more commonly in slow acetylators (Devadatta et al. 1960; Waldinger et al. 1984). To prevent the development of drug resistance during antituberculosis treatment, multiple drugs are given concurrently. Fast acetylators have been found to have lower concentrations of isoniazid, which may result in slower clearing of mycobacteria from the patient's sputum (Mitchell et al. 1958) and greater risk of isoniazid-resistant organisms appearing.

The importance of the isoniazid phenotype to the response to isoniazid in tuberculosis chemotherapy is largely dependent on the dosage regimen used. If the drug is given as part of a tuberculosis chemotherapeutic regimen administered daily, then acetylator phenotype does not appear to affect the likelihood of cure (Ellard 1976). On the other hand, if it is part of a once-weekly regimen, fast acetylators have a poorer response than slow acetylators (Ellard & Gammon 1977). A study in Singapore compared the sputum cultures of nearly 500 patients treated for tuberculosis with either high or low dose rifampicin (900 or 600mg, respectively), administered with isoniazid 15 mg/kg either once or twice weekly. Eight per cent of the individuals receiving the once-weekly low dose rifampicin accompanied by isoniazid were not cured, compared with only 3% on the higher dose once-weekly rifampicin and 0% on both the twice-weekly regimens (Singapore Tuberculosis Service/British Medical Research Council 1977). Thus, when isoniazid is used intermittently (once per week), fast acetylators appear to have a slightly higher rate of relapse than do slow acetylators.

Hepatitis develops in a proportion of patients receiving isoniazid. The frequency of hepatitis during isoniazid therapy was studied in 13 838 patients in a United States Public Health Service study which encompassed 21 cities. One of the striking and unexpected findings was that 30% of the hepatitis occurred in patients in Hawaii (Black et al. 1975), suggesting an interethnic difference in susceptibility. Because of the recognition that 80 to 90% of Orientals are fast acetylators (including those living in Hawaii) [table I], further investigations were performed to determine if the metabolism of isoniazid in fast acetylators might make them particularly susceptible to isoniazid-induced hepatitis. Mitchell et al. (1975) investigated the metabolism of the drug and found that greater amounts of acetylhydrazine were produced by fast acetylators: it appears that acetylhydrazine is converted to a reactive metabolite that can produce hepatic necrosis. However, more recent studies have not confirmed the increased susceptibility of fast acetylators to hepatotoxicity in India or Singapore (Gurumurthy et al. 1984; Singapore Tuberculosis Serv-

ice/British Medical Council 1977). This raises the question whether the increased rate of hepatotoxicity found in Hawaii is due solely to the interethnic difference in acetylation, or to some more complex ethnic effect.

Thus, by determining the frequency of the slow acetylation phenotype, ethnicity can be an important determinant of both the therapeutic response and the development of toxicity during therapy with drugs which are excreted by acetylation.

1.2 Polymorphism in Debrisoquine Metabolism

In the past 10 years cytochrome P450–dependent oxidation polymorphic traits have been described. The polymorphic metabolism of the antihypertensive debrisoquine and the antiarrhythmic and oxytocic drug sparteine were described independently by Mahgoub et al. (1977) and Eichelbaum et al. (1979). Subsequent studies have indicated that the ability to oxidise these 2 drugs is coinherited in Caucasians but not Ghanaians (Woodhouse et al. 1985). Family studies have shown that the defective oxidation of debrisoquine or sparteine is controlled by a single gene, and the poor metaboliser phenotype is homozygous for an autosomal recessive allele (Eichelbaum et al. 1982; Evans et al. 1980; Mahgoub et al. 1977).

There is considerable interethnic variability in the frequency of the poor metaboliser phenotype in different ethnic populations, ranging from 0 to 0.5% in a Japanese population (Horai et al 1989; Nakamura et al. 1985), 0 to 0.7% in a Chinese population (Horai et al. 1989; Lou et al. 1987), 1 to 1.4% in Egyptians and Saudi Arabians (Islam et al. 1980; Mahgoub et al. 1979) and 2% in a Hong Kong population (unpublished data, see Kalow 1984) to 6 to 10% in Caucasians, Nigerians and Ghanaians (table II). It was also reported that the frequency of this phenotype may be as high as 30% in a small Hong Kong Chinese population living in Canada (Kalow et al. 1980). This unusually high frequency of poor metabolisers may be a function of the fact that only 28 subjects were studied; alternatively, the fact that the less than optimal measure of metabolic ratio of drug and metabolite was used to screen poor and extensive metabolisers may have contributed to the difference (Kalow 1984).

The importance of the polymorphic oxidation of debrisoquine and sparteine lies in the large number of other drugs for which there is *in vivo* and/or *in vitro* evidence to suggest that they are also

Table II. Frequency of poor metabolisers of debrisoquine-type hydroxylation in populations

Population	No.	Frequency (%)	Reference
American Indian			
Panama	51	0	Arias et al. (1986)
Arab	102	1	Islam et al. (1980)
Black			
Ghana	154	0.7	Woolhouse et al. (1985)
	80	5	Woolhouse et al. (1979)
Nigeria	123	8	Mbanefo et al. (1980)
	116	3	Iyun et al. (1986)
Caucasian			
Britain	258	9	Evans et al. (1980)
	94	3	Mahgoub et al. (1977)
Germany	360	5	Eichelbaum et al. (1979)
Denmark	301	7	Brosen et al. (1985)
Switzerland	268	9	Schmid et al. (1985)
	222	10	Dick et al. (1982)
Sweden	226	8	Steiner et al. (1985)
	205	8.8	Sanz et al. (1989)
	757	5.4	Steiner et al. (1988)
Finland	107	6	Syvalähti et al. (1986)
Hungary	100	10	Gachályi et al. (1986)
Spain	124	10	Henthorn et al. (1989)
	377	6.6	Benitez et al. (1988)
Canada	83	7	Inaba et al. (1984)
US	156	7	Wedlund et al. (1984)
Australia	100	6	Peart et al. (1986)
Greenland	185	3	Brosen (1986)
Chinese			
Canada	13	31	Kalow et al. (1980)
China	269	0.7	Lou et al. (1987)
	98	0	Horai et al. (1989)
Egyptian	72	1.4	Mahgoub et al. (1979)
Japanese	100	0	Nakamura et al. (1985)
	200	0.5	Horai et al. (1989)

metabolised by this pathway (Jacqz et al. 1986). These include perhexiline, guanoxan, phenformin, propranolol, metoprolol, timolol, encainide, nortriptyline and propafenone (Kalow 1986). Therefore, the population frequency of genetically determined polymorphisms of certain oxidative biotransformation pathways may contribute to the substantial differences in responsiveness to some drugs, with a resultant significant difference in dosage requirements between ethnic groups such as Caucasians and Orientals.

1.3 Polymorphism in Mephenytoin Metabolism

The metabolism of mephenytoin exhibits polymorphism which is independent of debrisoquine hydroxylation (Jurima et al. 1984; Küpfer & Preisig 1984). Mephenytoin is used clinically as a racemic mixture of *S*- and *R*-enantiomers. The hydroxylation of the *S*-enantiomer is deficient in 3% of the Caucasian population (Küpfer et al. 1984; Wedlund et al. 1984), 17.4% in Chinese population and 22.5% in Japanese (Horai et al. 1989). The oxidation of mephenytoin is also inherited as an autosomal recessive trait (Inaba et al. 1986; Ward et al. 1987). *In vivo* and *in vitro* studies suggest that other drugs such as methylphenobarbital, diazepam, propranolol and warfarin may be metabolised by the same enzyme (Jacqz et al. 1986). The clinical consequences of this genetic enzymatic defect are complex and will require further study; however, the interethnic differences in the frequency of the poor metaboliser phenotype will be associated in different populations with altered response to drugs metabolised by this isozyme.

1.4 Polymorphism in Hydrolysis of Alcohol

Alcohol elimination appears to be under pronounced genetic control (Propping 1977), although the nature of the underlying genetic factors is still not well understood. Alcohol dehydrogenase (EC 1.1.1.1) and aldehyde dehydrogenase (EC 1.2.1.3) in the liver are the main enzymes responsible for ethanol oxidation in humans (Khanna & Israel 1980).

Alcohol dehydrogenase is responsible for the oxidation of about 90% of alcohol in the body. Its structure is controlled by 3 autosomal gene loci, ADH1, ADH2 and ADH3. Both ADH1 and ADH3 are active during fetal life, while ADH2 is responsible for most of the liver alcohol dehydrogenase activity in adults (Smith et al. 1971). Two forms of alcohol dehydrogenase, 'atypical' and 'usual', distinguished by catalytic activity, pH optima and pharmacokinetic parameters, have been described (Wartburg et al. 1965). The atypical form has greater alcohol oxidising activity and is polymorphically distributed in the population. In addition, there are interethnic differences in its distribution, with Japanese and Chinese individuals having a much higher frequency of the atypical allele (85 to 90%) [Fukui & Wakasugi 1972; Stamatoyannopoulos et al. 1975; Teng et al. 1979) than Caucasians (<5%) [Edwards & Evans 1967; Smith et al. 1971; Wartburg et al. 1968). It was initially suggested that the higher alcohol metabolism by this enzyme in Japanese and Chinese individuals might account for their propensity to develop adverse effects from alcohol, including the alcohol flush syndrome. However, it is now thought that abnormal aldehyde dehydrogenase is the most likely explanation.

It is well known that Orientals (including Chinese, Japanese and Koreans) are more sensitive to the adverse effects of alcohol, including marked facial flushing, palpitation and tachycardia. This increased sensitivity appears to correlate with increased acetaldehyde concentrations in susceptible individuals. The ability to metabolise acetaldehyde is also polymorphically distributed in populations, with interethnic differences in the frequency of the active enzyme. In around 50% of Japanese and Chinese individuals the active aldehyde dehydrogenase ($ALDH_2$) isozyme is missing (Harada et al. 1980; Mizoi et al. 1979; Teng 1981). As this isozyme is principally responsible for the oxidation of acetaldehyde, its absence results in increased acetaldehyde concentrations in affected individuals and explains their higher susceptibility to alcohol flush. Thus, interethnic differences in the frequency of

the isozyme responsible for the metabolism of acetaldehyde explain the increased frequency of adverse reactions to alcohol in Oriental populations who lack this isozyme. In addition it also may account for the decreased frequency of alcoholism in Orientals, in whom the genetic lack of ability to metabolise acetaldehyde normally produces an accumulation of acetaldehyde and therefore discourages overuse of alcohol.

The interethnic variability in the frequency of the poor metaboliser phenotype of various polymorphic drug metabolism traits is therefore an important determinant of interethnic variability in response. The alteration in response due to polymorphic drug disposition is due to changes in plasma drug concentrations. Because of the potential confounding effects of including differing proportions of poor metabolisers in studies of ethnic differences, it is particularly important to ensure that subjects are phenotyped and that the populations studied are comparable in their frequency of different phenotypes.

2. Ethnic Variability in Response to Cardiovascular Drugs

2.1 β-Receptor Blockers

There is marked interindividual variability in the plasma concentrations of the highly metabolised β-receptor blockers (Johnsson & Regårdh 1976). Much effort has been expended to ascertain and define the variables responsible for these differences. Age (Castleden et al. 1975; Vestal et al. 1979a), smoking (Vestal et al. 1979a), coadministration of other drugs (Feely et al. 1981; Vestal et al. 1979b; Zhou et al. 1990d), underlying disease processes (Lowenthal et al. 1974; Wood et al. 1978) and oxidation phenotype (Raghuram et al. 1984) have all been shown to affect the disposition of β-blockers. However, less attention has been paid to the influence of genetic factors and ethnicity on interindividual variability in the disposition and sensitivity of these drugs.

Venter and Joubert (1984) studied the effect of single intravenous doses of propranolol on exercise-induced rise in heart rate, and showed that after 30 minutes the reduction in heart rate following 6, 8 and 10 minutes of bicycle exercise was greater in Whites than in Blacks (fig. 1). From this study it was not possible to determine if the differences were due to differences in sensitivity or in the disposition of propranolol between the 2 groups. Subsequently, the same authors examined the phar-

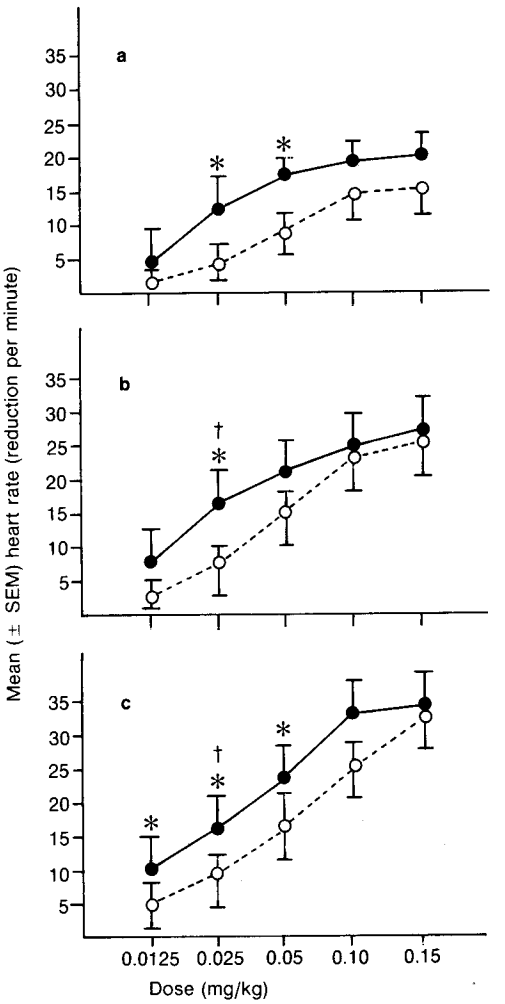

Fig. 1. Effect of single intravenous injections of increasing doses of propranolol on the reduction in exercise heart rate after (**a**) 6, (**b**) 8 and (**c**) 10 minutes of exercise in White (●) and Black (○) subjects: * = $p < 0.05$ (paired t-test); † = $p < 0.05$ (unpaired t-test) [from Venter & Joubert 1984a, with permission].

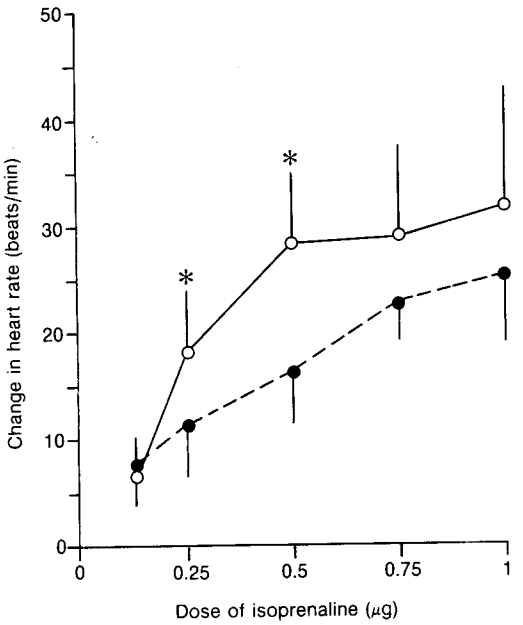

Fig. 2. Increase in heart rate in response to intravenous infusion of isoprenaline (isoproterenol) in Black (○) and White (●) subjects; * $p < 0.05$ (from Rutledge et al. 1989a, with permission).

macokinetics of intravenous propranolol in Blacks and Whites and could find no difference, implying that the interethnic differences in response which they had seen must have been due to changes in sensitivity rather than in drug disposition (Venter et al. 1985a).

In subsequent studies the effects of the combination of atropine and propranolol were studied in 8 Black and 8 White volunteers, and the intrinsic heart rate was found to be significantly higher in Blacks (Venter et al. 1984). Later, the same group compared the effects of both bisoprolol and propranolol in both races, but this time calculated the suppression of exercise-induced tachycardia in terms of the difference in heart rate during exercise (corrected for their heart rate) after atropinisation. Using this technique they failed to find a difference in sensitivity (Joubert et al. 1988). They therefore concluded that the altered sensitivity to β-blockade was due to the greater parasympathetic tone in Black individuals.

Sensitivity to β_1-agonists may also be altered in Blacks so that the change in heart rate in response to increasing doses of isoprenaline (isoproterenol) is greater than in Whites (fig. 2) [Rutledge et al. 1989a]. Conversely, the same group of investiga-

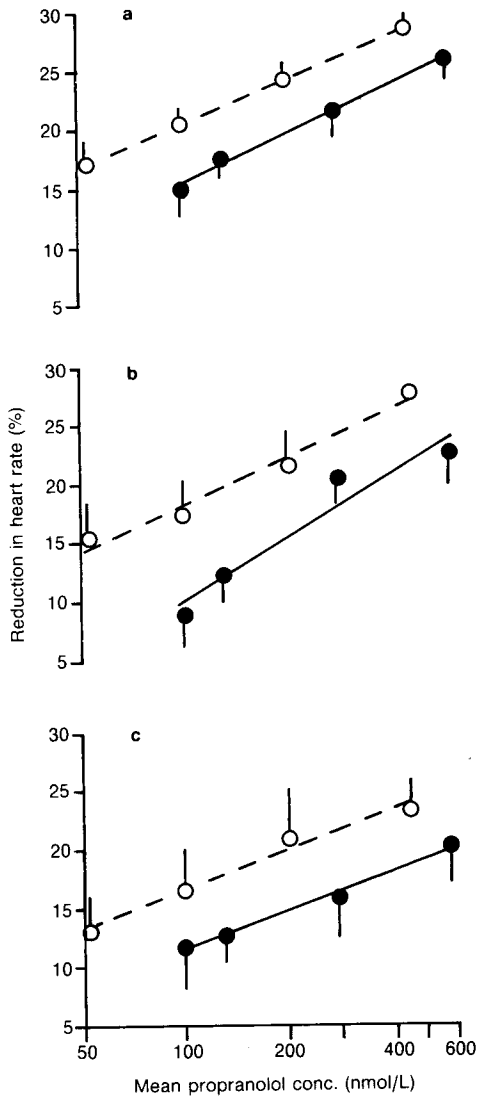

Fig. 3. Concentration-response curve for propranolol (**a**) during exercise, (**b**) upright and (**c**) supine, in Chinese (○) and Caucasian (●) subjects (from Zhou et al. 1989a, with permission).

tors using the β-receptor antagonist metoprolol showed that the predicted maximum effect (E_{max}) for β-blockade was higher in Blacks than in Whites at similar plasma metoprolol concentrations (Rutledge et al. 1989b).

In keeping with these *in vivo* studies demonstrating increased sensitivity to β_1 stimulation in Blacks are some of the *in vitro* findings in human lymphocytes. Higher concentrations of isoprenaline were required to increase cyclic adenosine monophosphate (cAMP) levels in lymphocytes from Whites to the same extent as the levels in Blacks (Venter et al. 1985b). In contrast, in a preliminary report Stein et al. (1987) found that stimulation of cAMP by isoprenaline was lower in Blacks than Whites.

In clinical practice, Chinese patients empirically receive much lower doses of propranolol for the treatment of hypertension and arrhythmias because of the clinical impression that Chinese patients are particularly sensitive to β-blockade. The widespread use of β-blockade in the treatment of a range of conditions makes it particularly important that interethnic differences be clearly defined.

Because of the lower dosage of propranolol used in Chinese patients, we have compared the disposition and pharmacodynamics of propranolol in Chinese and Caucasians (Zhou et al. 1988, 1989a). We found that in comparison with Caucasians the concentration-response curves relating reduction in heart rate and propranolol concentration in Chinese were shifted significantly to the left; this was true during upright and supine posture, and exercise (fig. 3). The propranolol concentration required to produce a 20% reduction in heart rate (IC_{20}) was lower in Chinese than in Caucasians, implying that to produce the same degree of β-blockade Caucasian individuals required plasma propranolol concentrations at least twice as high as Chinese. The increased sensitivity to β-blockade produced by propranolol in Chinese patients is still seen even in the absence of vagal activity by means of atropinisation (Zhou & Wood 1990a). Again the concentration-response curves for reduction in mean blood pressure in the Chinese population were significantly to the left of those in Caucasians (fig. 4) and the IC_{10} for Chinese was 4.5- to 10-fold lower than that in Caucasian patients for both supine and upright positions (Zhou et al. 1989a). Thus, Chinese individuals appear to be more sensitive to both the β-blocking and hypotensive actions of propranolol.

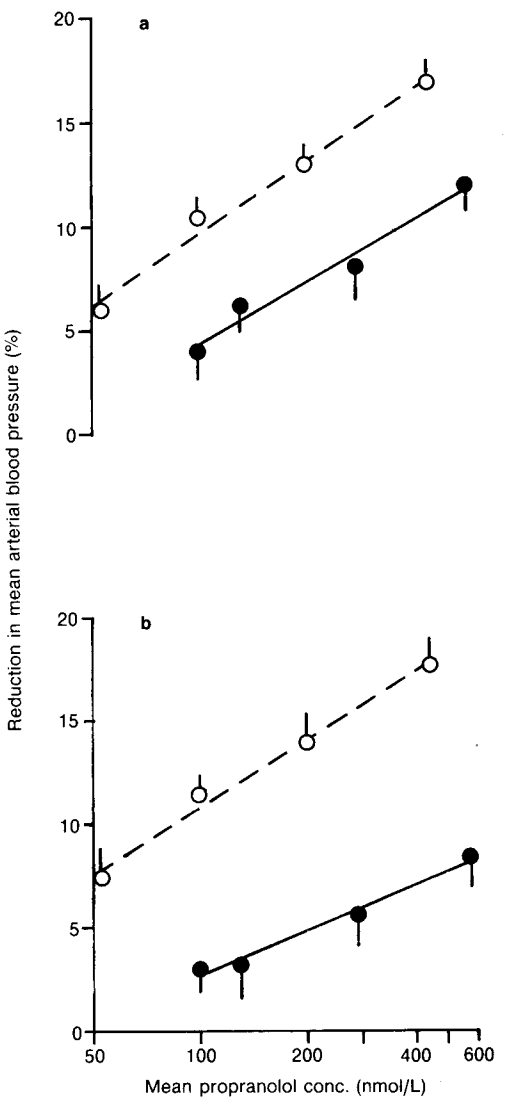

Fig. 4. Blood pressure reduction in response to propranolol, (a) upright and (b) supine, in Chinese (O) and Caucasian (●) subjects (from Zhou et al. 1989a, with permission).

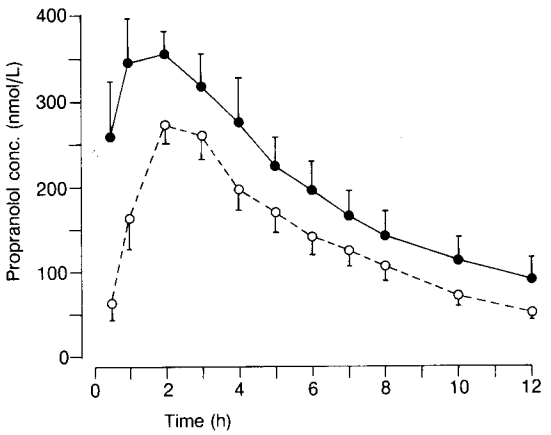

Fig. 5. Plasma propranolol concentrations in Chinese (○; n = 10) and Caucasian (●; n = 9) subjects (from Zhou et al. 1989a, with permission).

In addition to the pharmacodynamic differences outlined above, there were also marked pharmacokinetic differences between the 2 populations. The plasma propranolol concentrations were lower in the Chinese individuals than in the Caucasians (fig. 5), resulting in an elevated plasma propranolol clearance (table III). In addition, the clearance of propranolol both by 4-hydroxylation and by glucuronidation were higher in the Chinese patients (table III). The difference in clearance was even more marked when the total clearance was corrected for the different bodyweights of the 2 populations. Since the clearance of propranolol is higher in Chinese than in Caucasians, pharmacokinetic differences do not account for the increased sensitivity seen in the former. Although we found that the plasma concentration of 4-hydroxy-propranolol, the pharmacologically active ring oxidised metabolite, was significantly higher in the Chinese patients after propranolol 80mg orally (table III), we think it unlikely that this accounts for the greater β-blockade in these individuals. In a previous study we have shown that a 5-fold difference in 4-hydroxy-propranolol concentrations did not produce an alteration in the extent of β-blockade (Raghuram et al. 1984) and the less than 2-fold higher concentrations seen in these Chinese individuals would be unlikely to account for the greater β-blockade.

Binding to plasma proteins is one of many factors affecting the pharmacodynamics of drugs. Since it is only the free concentration of a drug which is available for binding to receptors and producing the pharmacological effect, alteration in the free or unbound fraction in plasma may alter drug effect. Genetic factors have been found to influence the extent of plasma protein binding of some drugs (Alexanderson & Borga 1972; Iselius et al. 1978; Wilding et al. 1977). In the case of propranolol binding, genetic factors are thought to be more important than environmental factors (Alván et al. 1983). The percentage of unbound propranolol was significantly higher in Chinese than in Caucasians, which was associated with a lower α_1-acid glycoprotein level in the former, a major determinant of plasma protein binding of this drug (Zhou & Wilkinson 1990; Zhou et al. 1989a). Furthermore, the ratio of unbound (−) to (+) propranolol was greater in Chinese than in Whites, implying that

Table III. Mean (± SEM) disposition of oral propranolol 80mg in Chinese (n = 10) and Caucasian (n = 9) subjects (data from Zhou et al. 1989a)

	Chinese	Caucasian
AUC (nmol/L • h)		
propranolol	1797 ± 266	3193 ± 864*
4-OH-propranolol	228 ± 27	131 ± 23*
naphthoxylactic acid	15 760 ± 1866	9871 ± 1014*
CL (L/h)	224.4 ± 44.2	127.5 ± 12.8*
(L/h/kg)	3.6 ± 0.8	1.6 ± 0.2*
$t_{1/2}$ (h)	4.0 ± 0.3	5.1 ± 1.2
$CL_{P,m}$ (L/h)		
propranolol glucuronide	20.2 ± 3.8	11.7 ± 1.7*
total 4-OH-propranolol	30.9 ± 5.8	11.8 ± 3.5**
naphthoxylactic acid	9.5 ± 0.9	7.9 ± 0.4

Abbreviations: AUC = area under the concentration-time curve; CL = total clearance; $t_{1/2}$ = half-life; $CL_{P,m}$ = partial metabolic clearance.

Significant differences between the groups: * $p < 0.05$; ** $p < 0.01$.

there is a proportionately greater unbound fraction of the pharmacologically active (−) isomer in Chinese patients (Zhou et al. 1991). Thus, the increased free fraction of both propranolol and (−) propranolol in Chinese subjects may make some contribution to their increased sensitivity. However, as the increase in the free fraction was much smaller than the increase in sensitivity to either the negative chronotropic effects of propranolol or the hypotensive effect, it clearly does not explain all of the change seen.

Cardiac sensitivity to β-adrenergic agonists in humans is correlated with β-adrenergic receptor density on lymphocytes from the same individuals (Fraser et al. 1981). It appears that the β-blockade produced by propranolol is determined by the density of β-adrenergic receptors on lymphocytes and leucocytes (Tawara et al. 1987; Zhou et al. 1989b). However, Zhou et al. (1989a) showed that β-receptor density and affinity for the antagonist 125-IPIN on lymphocytes did not differ between Chinese and Caucasian individuals. Thus, changes in receptor density or affinity do not explain the increased sensitivity to β-adrenergic blockade.

The propranolol used clinically is a racemic mixture of the *dextro* (+) and *levo* (−) isomers. The β-receptor blocking activity of the latter is over 100 times that of the former (Murray et al. 1990), so that the concentrations of the (−) isomer are the principal determinants of the extent of β-blockade produced. Thus, a possible explanation for the increased sensitivity to propranolol found in Chinese patients might be that a higher proportion of their total propranolol concentrations is composed of the more active (−) isomer than is found in Caucasians. To examine this possibility, Zhou and Wood (1990b) determined the concentrations of the 2 propranolol isomers in both populations. They confirmed that the clearance of the more active (−) isomer was lower (and hence the concentrations were higher) than was found for the less active (+) isomer. However, Chinese and Caucasians did not differ in their ratio of (+) : (−) propranolol, implying that the differences in total concentrations of propranolol measured in the 2 populations reflected similar ratios of the isomers, so that differential enantioselectivity cannot explain the sensitivity difference.

Zhou and Wood (1990c) recently reported that propranolol suppresses the exercise-induced rise in renin more in Chinese patients than in Caucasians. The exercise plasma renin activity was 40% higher in the former. However, after administration of single oral doses of propranolol 10, 20, 40 and 80mg the reduction in plasma renin activity was 140% greater. The lowering in mean blood pressure correlated with this reduction. A greater suppression of renin may contribute to the higher sensitivity to the hypotensive effect of propranolol in the Chinese population.

2.1.1 Consequences of Debrisoquine Polymorphism on the Disposition and Response of β-Blockers

The polymorphism of debrisoquine metabolism is discussed above (section 1.2). About 5 to 10% of the Caucasian population (Brosen et al. 1985; Dick et al. 1982; Eichelbaum et al. 1979; Evans et al. 1980; Peart et al. 1986; Schmid et al. 1985; Steiner et al. 1985; Syvälahti et al. 1986; Wedlund et al. 1984) and about 0 to 0.7% of the Japanese and Chinese have an impaired ability to eliminate debrisoquine and are termed poor metabolisers (Horai et al. 1989; Luo et al. 1987; Nakamura et al. 1985). The polymorphic ability to oxidise debrisoquine is a major factor in determining the pharmacological and toxicological effects of many drugs, including β-blockers. *In vivo* and *ex vivo* studies have shown that the metabolism of a number of β-blockers including alprenolol, bufurolol, labetolol, metoprolol, oxprenolol, pindolol, propranolol and timolol cosegregate with the polymorphic ability to metabolise debrisoquine (Alván et al. 1982; Ayesh et al. 1984; Boobis et al. 1985; Dayer et al. 1982; Distlerath et al. 1985; Inaba et al. 1985; Lennard et al. 1982a,b; McGourty et al. 1985a,b; Otton et al. 1983; Raghuram et al. 1984; Silas et al. 1985).

The pharmacokinetic consequences of polymorphism of the metabolism of β-blockers varies with the contribution that the debrisoquine isozyme makes to the overall clearance of the drug. Poor metabolisers of debrisoquine have been shown

to produce much less 4-hydroxy-propranolol than do extensive metabolisers, and this ability has been shown to correlate with the ability to hydroxylate debrisoquine (Lennard et al. 1984; Raghuram et al. 1984). However, poor and extensive metabolisers do not differ in their propranolol concentrations, nor was any difference seen in the extent of β-blockade between the 2 phenotypes. This was because, although 4-hydroxylation of propranolol is minimal in poor metabolisers, this pathway contributes only 9% (in Caucasians) to 14% (in Chinese) to the overall clearance of propranolol (Zhou et al. 1989a).

Presumably because the affected pathway is a more major contributor to the overall drug clearance of metoprolol, bufuralol and timolol, poor metabolisers have increased concentrations, a prolonged elimination half-life and a more intense and sustained pharmacological effect after single doses of these drugs (Dayer et al. 1983; Lennard et al. 1982a,b; Lewis et al. 1985). Since the frequency of impaired 4-hydroxylation (table II) of debrisoquine exhibits considerable interethnic variability, it would be expected that there will be a major difference in the effects of the drugs in different ethnic populations due to their different proportions of the 2 phenotypes.

2.1.2 β-Receptor Blockers in Hypertension

One of the major determinants of the response to β-blockers in hypertension is the individual's renin status: people with high renin respond to lower doses of β-blocker (Hollifield et al. 1976). Interethnic differences in renin status are therefore important in determining the likelihood that an individual will respond to a β-blocker – or for that matter other drugs, such as angiotensin-converting enzyme (ACE) inhibitors, which act through a renin-dependent mechanism.

A greater proportion of Whites than Blacks have elevated plasma renin activity (PRA). Thus, it might be predicted that a difference in response to single-drug therapy would be seen between Black and White patients. This issue has been examined by the Veterans Administration Cooperative Study Group on Antihypertensive Agents (1982a) in a double-blind study of 683 men with diastolic blood pressures between 95 and 114mm Hg receiving propranolol (n = 340) or hydrochlorothiazide (n = 343).

Table IV. Effects of race in a study of 683 men with diastolic blood pressure (DBP) between 95 and 114mm Hg receiving propranolol (n = 340) or hydrochlorothiazide (n = 343) [Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982a]

Race	Propranolol	Hydrochlorothiazide	p-Value[a]
Patients achieving DBP < 90mm Hg (%)			
White	61.7	55.3	NS
Black	53.3	71.3	<0.001
Reduction achieved (mm Hg)			
White	−12.6 ± 6.6	−10.9 ± 5.7	< 0.02
Black	−9.5 ± 7.0	−13.0 ± 7.0	< 0.001

a Significant differences between drugs.

The proportion of White patients (table IV) who achieved their blood pressure goal (diastolic pressure < 90mm Hg) was 6.4% higher on propranolol than on hydrochlorothiazide, although this difference was not significant. On the other hand, 18% more Black patients achieved their goal on the diuretic than on the β-blocker ($p < 0.001$, table IV). The absolute reduction in diastolic blood pressure followed the same direction, so that in Whites there was a significantly greater fall in diastolic pressure on propranolol while in Blacks there was a significantly greater fall on diuretic (table IV). These data are in keeping with the finding that Blacks tend to have lower plasma renin levels than Whites, but they deserve further discussion. It should be emphasised that though there were significant differences in the proportion of Black and White patients responding to each drug, interpretation of these data should not be carried too far. It is sometimes implied that Blacks do not respond to β-blockers, while Whites respond poorly to diuretics as first-line therapy. As the data in table III show, at least 50% of patients responded to their less effective therapy whatever their race. Conversely, even in the case of Black patients the difference in the frequency of response between the 2 treatments was only 18%.

An extension of the above study examined the effects of long term therapy in the smaller number of patients who went on to it, and suggested that there were no racial differences in the long term response of diastolic blood pressure to either β-blocker or diuretic. However, systolic blood pressure fell more in Whites with propranolol than it did in Blacks (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982b). A problem with this study, however, is that not all patients went on to receive long term therapy and, the groups consequently containing different numbers of subjects receiving each drug, definitive interpretation is difficult.

Other studies have looked at β-blocker therapy for hypertension in Blacks in Zimbabwe (Abson et al. 1981), South Africa (Seedat 1980) and Jamaica (Humphreys & Delvin 1968) and also found little reduction in blood pressure with β-blockade, in keeping with the suggestion that Blacks are less responsive than Whites to these drugs as first-line therapy for hypertension.

2.2 α_1-Receptor Blockers

A number of drugs such as prazosin, trimazosin and terazosin act by antagonising the effects of norepinephrine (noradrenaline) at α_1-adrenergic receptors. Although interethnic differences in α_1 responsiveness have been studied much less than interethnic responsiveness to β-adrenergic agonists and antagonists, it appears at least with trimazosin that there is no marked difference between Caucasians and West Africans in their response to α_1-blockade (Vincent et al. 1986). There were, however, modest pharmacokinetic differences, with the Caucasians having a larger volume of distribution for trimazosin and a longer terminal elimination half-life for the active metabolite 1-hydroxytrimazosin. The hypotensive effects of trimazosin correlate to the blood concentrations of both parent drug and the metabolite (Meredith et al. 1983). The altered volume of distribution of trimazosin probably reflects differences in tissue or plasma protein binding.

On the other hand labetalol, a drug with both β- and α-adrenergic blocking properties (Goa et al. 1989), produced a significant reduction in blood pressure only in Caucasians (in contrast to either Africans or West Indians), confirming the interethnic differences in the response to β-blockade, discussed above, which was the principal determinant of the effect of labetalol in this population (Jennings & Parsons 1976).

2.3 Angiotensin-Converting Enzyme (ACE) Inhibitors

The effects of ACE inhibitors are dependent on the individual's renin status. High renin individuals have a greater hypotensive effect from ACE inhibition than do low renin patients. In keeping with the differing response to β-blockers seen in Blacks and Whites because of their differing renin status are the findings with the ACE inhibitor captopril. White patients had a systolic and diastolic blood pressure reduction of 14.7 ± 1.1 and 10.7 ± 0.6mm Hg, respectively, while the blood pressure of Black patients fell by only 9.1 ± 1.2 and 8.0 ± 0.7mm Hg, respectively, showing that White patients respond to captopril better than Black patients. When hydrochlorothiazide was added to captopril the racial difference in response was abolished (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982b). Thus, the response to ACE inhibition also appears to be racially influenced, probably on the basis of renin or volume-dependent status.

2.4 Ketanserin

Ketanserin is a serotonin$_2$ (5-hydroxytryptamine$_2$)-receptor antagonist with antihypertensive effects (Brogden & Sorkin 1990). In a study of 16 patients (9 Black and 7 White), ketanserin significantly lowered blood pressure in the White patients although it was not significantly altered in Blacks (Cressman et al. 1987). Although PRA was significantly higher in Whites (2.7 ± 2.1 *vs* 0.8 ± 0.7 μg/L • h, respectively) this does not account for the racial differences, as no relationship was found

between the pretreatment plasma renin activity and the extent of blood pressure response.

2.5 Atropine

As long ago as 1921, Paskind reported that the initial bradycardia after parenteral administration of atropine does not occur in American Negroes at doses which caused a bradycardia in matched White controls. After 20 American Negroes received atropine 1/60 grain subcutaneously, 14 of the 20 volunteers did not show any reductions in heart rate. In the remaining 6 volunteers, the greatest reductions in heart rate were only 2 to 4 beats/min. However, in 18 of 20 White volunteers the slowing of the heart rate was more marked, with the greatest reduction being between 4 and 16 beats/min. In only 2 of the Whites was there no reduction in heart rate. Recently, a study from South Africa reported that, after the administration of atropine 0.5mg, African Negroes were also resistant to the initial bradycardic effect of atropine but were more susceptible to the late bradycardic effect which occurs about 1h after the dose. The tachycardia effect was also significantly more pronounced in Blacks than in Whites (Meyer et al. 1988).

Zhou and Wood (1990e) reported that after intravenous atropine 0.003, 0.006, 0.012 and 0.024 mg/kg, healthy Chinese volunteers had a greater increase in heart rate than Caucasians. The bradycardic effect occurred in all subjects after a dose of 0.003 mg/kg, with no difference between the 2 populations; these results may reflect either a true difference in sensitivity to the early effects of atropine or a pharmacokinetic difference.

3. Variations in Effects of CNS Drugs

3.1 Benzodiazepines

The doses of diazepam used in Hong Kong Chinese are said to be lower than those prescribed for Caucasians, due to a perception that the Chinese have an increased sensitivity to its sedative effects (Kumana et al. 1987). The pharmacokinetics and pharmacodynamics of diazepam 0.2 mg/kg intravenously were compared in a group of Caucasians and Orientals (Ghonein et al. 1981) and a number of psychological tests were used to assess performance, including digit recall, self-assessment of sedation and arithmetic skills. Both the Oriental and Caucasian volunteers showed a maximal effect at 30 minutes after administration but no differences were detected in the effects between the 2 groups.

The concentrations of both diazepam and the metabolite demethyl-diazepam tended to be higher in the Orientals, as reflected by a significantly lower clearance when corrected for weight in the Orientals. Although non–weight-corrected clearance did not differ between the 2 groups there was a trend towards a higher volume of distribution in the Caucasians. However, no significant difference in this parameter was seen when corrected for bodyweight.

In an additional study of the pharmacokinetics of oral diazepam (Kumana et al. 1987) there was a trend towards a higher apparent volume of distribution in the Caucasians than in the Chinese. This apparent ethnic difference was largely due to a different level of obesity, which was higher among the former.

The pharmacokinetics of alprazolam have been compared in Caucasians and Asians born either in or outside the US (Lin et al. 1988a). Plasma concentrations were significantly higher in the Asians, resulting in their having significantly lower clearances of alprazolam independent of their place of birth. Again, the differences remained even when corrected for the differences in surface area between the 2 groups.

It appears from the above studies that the concentrations of benzodiazepines may be higher in Asians than in Caucasians; however, the pharmacodynamic effects of these differences remain to be demonstrated.

3.2 Amobarbital (Amylobarbitone)

Amobarbital is mainly metabolised to 3′-hydroxy-amobarbital (a product of side-chain hydroxylation) and *N*-β-*D*-glucopyranosyl-amobarbital (*N*-glu), in which a glucose molecule is at-

tached to the ring nitrogen. The ratio of the 2 major metabolites in urine shows considerable interindividual variability (Kalow et al. 1978). There appears to be a racial difference in the metabolite disposition of amobarbital, with Caucasians having a higher concentration of the side-chain oxidation product in their urine than do Orientals, while the latter had a higher concentration of *N*-glu (Kalow et al. 1979). The results indicate that Oriental individuals had a greater capacity for *N*-glucosidation rather than C-hydroxylation of amobarbital, compared with Caucasians. However, the pharmacodynamic consequence of this difference, if any, has not been defined.

3.3 Tricyclic Antidepressants

The dosage level of antidepressants appears to be substantially lower in Asia than that customarily used in Western countries. A survey by Yamashita and Asara found that psychiatrists in 10 Asian countries reported using much lower doses of both imipramine and amitriptyline than those used in the US. However, the plasma concentrations appeared to be appropriate for the lower doses. Smaller doses of antidepressants also appear to be given to Asian patients within the US (Yamamota et al. 1979).

There is an impression that Asians drawn from the large Asian population in Bradford, England, are less tolerant of tricyclic antidepressant side effects than Caucasians. In a study comparing Bradford residents of Asian and English origin (Allen et al. 1977) there appeared to be a dose-related increase in side effects in both Asian and English individuals receiving first placebo, then clomipramine 25mg and finally clomipramine 30mg. However, the dose-response relationship was more striking for the Asian group, in whom the increase was greater and was matched by an approximately 50% increase in clomipramine concentrations (Allen et al. 1977). The same researchers in a later publication (Lewis et al. 1980) included a larger English group but what appears to be the same Asian subjects, and found that the previously described differences in plasma concentration persisted.

Table V. Characteristics of female Hispanic (n = 41) and Anglo (n = 21) patients treated for depression with tricyclic antidepressants (after Marcos & Cancro 1982)

	Hispanic	Anglo
Maximum daily dose (mg)		
All tricyclics	66.14 ± 33.80	130.95 ± 46.31
Amitriptyline	64.28 ± 24.71	125.00 ± 52.43
Imipramine	85.00 ± 33.91	137.50 ± 21.53
Doxepin	57.00 ± 41.12	135.71 ± 46.02
Effect of treatment (%)		
All side effects	78	33.3
Discontinued because of side effects	17	4.8
Therapeutic outcome		
improved	75.6	71.4
unchanged or worse	7.4	23.8

Marked differences have been described in both the frequency and characteristics of psychiatric diseases between Hispanic and Anglo individuals in the US (Marcos & Cancro 1982). In a study of female patients treated at 2 New York hospitals, those authors compared the characteristics of a group of 41 Hispanic and 21 Anglo patients treated for depression. The doses of tricyclics used in the 2 groups are shown in table V. The Hispanic patients received significantly lower doses of tricyclics than Anglo patients. Of additional interest (table V) was the finding that, despite the lower doses, more of the Hispanic patients developed side effects and consequently more discontinued treatment. Conversely, more of the Anglo patients were seen as deriving no benefit from the antidepressant medication (table V).

This study might suggest that Hispanic patients have higher concentrations of tricyclic antidepressants; however, Gaviria et al. (1986) studied the pharmacokinetics of nortriptyline in Hispanic and Anglo patients of both sexes and found that, although there were substantial interindividual differences, there appeared to be no ethnic difference which could explain the pharmacodynamic variability described above.

A cross-cultural study comparing depressed

patients treated in Colombia and the US found that, with slightly higher doses of imipramine in Colombian patients, significantly more developed side effects and/or improved on therapy in comparison with the US patients (Escobar & Tuason 1980).

Higher concentrations of tricyclic drugs are found in Blacks than in Whites; for example, Ziegler and Biggs found amitriptyline concentrations to be 84.2 and 66.2 μg/L in the 2 populations, respectively. The same trend was seen with nortriptyline: significantly higher concentrations were found in Blacks (113.5 μg/L) than in Whites (75.7 μg/L). Similar findings have been reported following overdosage of tricyclics. In a study of 19 patients after overdose, the total concentrations tended to be higher in the 6 Black patients (Rudorfer & Robins 1982) despite the 12 White patients having taken a larger amount of drug.

The difference between the doses of antidepressants used in Asian patients appears to extend to the use of lithium, which is customarily prescribed in lower doses in Japan than in the US. These lower doses appear to produce the same level of efficacy, but plasma lithium concentrations are lower in Japan (thus implying a higher sensitivity) [Takahashi 1979].

In summary, Asians and Hispanics appear to respond to lower doses and have lower effective concentrations of antidepressants than Anglos. These findings suggest that there is increased tissue sensitivity to antidepressants in these non-Anglo groups. However, the effects of cultural differences in expectation of the effects of medication cannot be ruled out.

3.4 Neuroleptic Agents

Haloperidol is widely used in treatment of psychiatric disorders, including schizophrenia (Beresford & Ward 1987). It has been reported that mean dosages were significantly lower in Chinese psychiatric patients than in non-Chinese patients (fig. 6) [Jann et al. 1989]. The pharmacokinetics of haloperidol following both intramuscular and oral administration have been studied (Lin et al. 1988b) in 3 groups - Caucasians, Asians born in the US and Asians born elsewhere. The maximum drug concentrations after intramuscular administration were higher in the Caucasian group in comparison to the Asians wherever they were born (fig. 7), with little difference in concentration thereafter. A greater difference between the 2 ethnic groups was seen following oral administration, implying that absorption may be lower or first-pass metabolism greater in the Caucasians. Although the differences were less after systemic (intramuscular) administration they were still apparent, suggesting that absorption could not account for them all.

By producing pituitary dopamine receptor blockade, haloperidol causes a rise in prolactin levels, which was used as a measure of the sensitivity to haloperidol effects. As can be seen from figures 7 and 8, the prolactin concentrations were substantially lower in Caucasians than in either of the Asian groups after both intramuscular and oral administration. After intramuscular administration the differences appear particularly striking. These differences in the prolactin response to haloperidol remained apparent even when variations in haloperidol concentration following intramuscular administration were taken into account. Thus, this study provides important objective evidence for the increased sensitivity to haloperidol in Asian patients. In addition, the principal factor accounting for these differences appears to be genetic rather than environmental because of the similarity between the 2 groups of Asians.

In a group of Chinese schizophrenic patients matched for sex and bodyweight to a group of US Black and White patients, Potkin et al. (1984) found after 6 weeks of repeated-dose therapy with haloperidol that the Chinese patients in the People's Republic of China had plasma drug concentrations 52% higher than the US patients. These findings are similar to the findings of Lin et al. (1988b) described above. The incidence of extrapyramidal reactions following haloperidol is increased to 95% in Asians (Chinese, Japanese and Korean), but only 60% in Blacks and 75% in Whites, implying that Asians are also more sensitive to the extrapyramidal effects of haloperidol (Binder & Levy 1981). A higher incidence of extrapyramidal reactions in

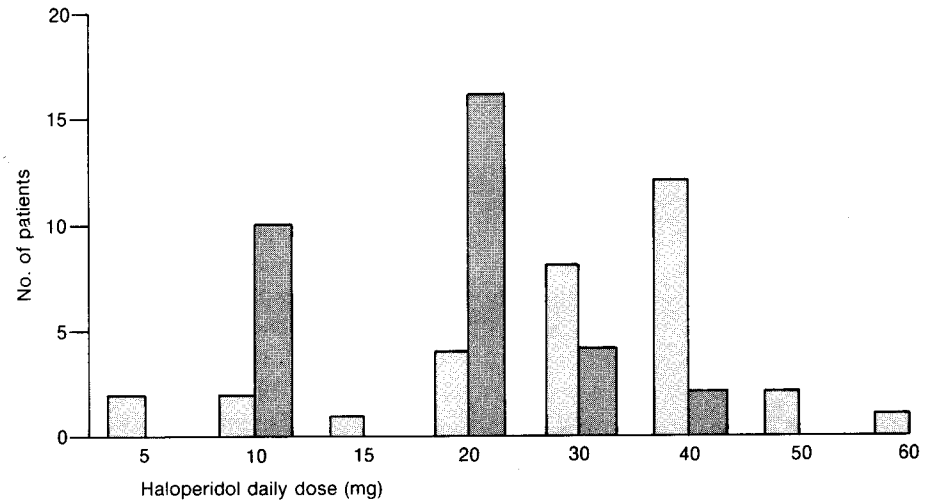

Fig. 6. Frequency distribution of haloperidol dosages in Chinese (■) and non-Chinese (□) patients (from Jann et al. 1989, with permission).

Chinese (56%) than in non-Chinese (Hispanic, Black and White) patients (36%) was also reported by Jann et al. (1989).

Reduced haloperidol is a major metabolite of haloperidol which undergoes a reduction/oxidation cycle with the parent drug. The total haloperidol clearance could be influenced by the reduced haloperidol : haloperidol ratio and the rate of oxidation of the metabolite back to the parent compound (Jann et al. 1989). Chang et al. (1987) reported a lower ratio of reduced haloperidol : haloperidol in Chinese schizophrenic patients (0.31 ± 0.24) than White patients (about 1). Jann et al. (1989) also reported that the reduced haloperidol levels were 3 times greater in non-Chinese than in Chinese patients (16.3 ± 18.5 *vs* 5.3 ± 4.3 μg/L). The lower plasma reduced haloperidol concentration in the Chinese group suggests a decreased reducing activity. Therefore, the different haloperidol concentrations and sensitivity to the drug in different ethnic populations may reflect a difference in reducing activity.

Asians also appear to be more sensitive to other antipsychotic agents. The dose of chlorpromazine used in Japanese patients to treat mania is also substantially lower than that used in Caucasians (Okuma 1981). In a retrospective review of 13 Asian patients who received neuroleptics in hospital and 13 White patients who were matched for age, sex, diagnosis and date of discharge, the maximum dose and dose of neuroleptic at discharge were compared: the doses of neuroleptic required in the White patients were substantially higher (table VI). This was true for both the maximum and long term dosages and, moreover, when the doses were corrected to a standard weight of 68kg these differences remained (table VIII) [Lin & Finder 1983). In addition, despite the lower doses used in the Asian patients, a similar proportion of Asian (69%) and White patients (77%) developed extrapyramidal symptoms; however, the dose associated with the first appearance of the symptoms was only 574 mg/day for the Asians but 1079 mg/day for the Whites.

A number of other studies have highlighted the low doses of neuroleptic drugs required in Asians (Yamamota et al. 1979). Thus, it appears that Asians respond to lower doses of neuroleptic drugs than Whites and they develop toxicity at lower doses. Part of the difference may be due to pharmacokinetic differences resulting in higher plasma concentrations but, even when the results are cor-

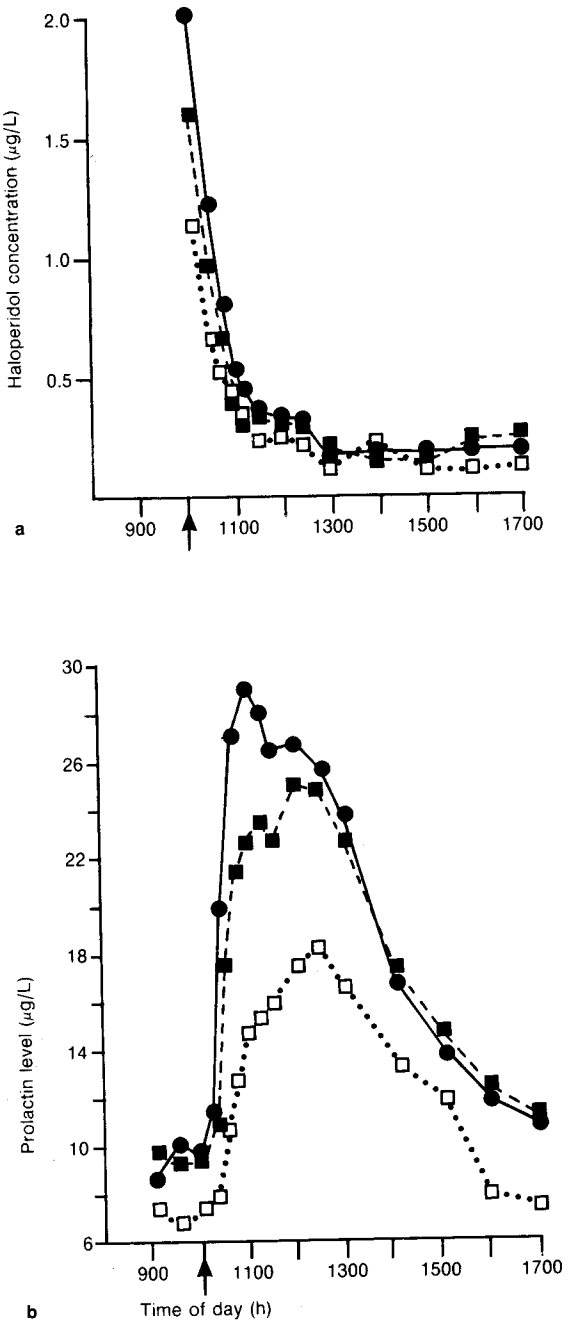

Fig. 7. (**a**) Serum haloperidol concentrations after an intramuscular dose of haloperidol 0.5mg in 12 Caucasians (□), 11 American-born Asians (■) and 11 Asians born elsewhere (●). (**b**) Serum prolactin levels after the same dose; ↑ = time of dose (from Lin et al. 1988b, with permission).

rected for concentration, Asians appear to be more sensitive to neuroleptics.

3.5 Diphenhydramine

The pharmacokinetics of diphenhydramine differ in Oriental and Caucasian populations (Spector et al. 1980). Following both oral and intravenous administration, plasma diphenhydramine concentrations are higher in the latter, due to a higher clearance in Orientals. In addition to the change in clearance, volume of distribution is also increased in the Orientals (probably because of their higher free fraction). The lower plasma concentrations in Oriental patients were associated with less sedation.

Zhou and Wilkinson (1989) compared the binding of diphenhydramine in plasma obtained from healthy Chinese and Caucasian subjects. The percentages of unbound drug were significantly higher in the Chinese group (26.4 ± 6.5 *vs* 18.3 ± 4.31%). This was associated with a lower α_1-acid glycoprotein level (350 ± 121 *vs* 598 ± 155 mg/L, respectively). The reason for the difference in α_1-acid glycoprotein levels between Chinese and Caucasians is not clear. Binding to plasma protein restricts the extravascular distribution of drugs, and is also an important determinant of the systemic clearance of a drug. Therefore, the higher free fraction of diphenhydramine in Chinese individuals could explain the greater volume of distribution and higher clearance of this drug compared with Caucasians, as reported by Spector et al. (1980).

3.6 Levodopa

When levodopa is administered for the treatment of Parkinson's disease, it is not only converted to dopamine by decarboxylation but is also metabolised to 3-*O*-methyldopa by catechol-*O*-methyltransferase (COMT). In studies of patients receiving levodopa the metabolite 3-*O*-methyldopa appears to antagonise the therapeutic effects of the parent drug in patients with Parkinson's disease (Muenter et al. 1973), and therefore the greater the

activity of COMT (and hence the larger the amount of 3-*O*-methyldopa produced) the less favourable is the response to levodopa (Reilly et al. 1980; Rivera-Calimlim et al. 1977).

The activity of the red cell enzyme (COMT) is bimodally distributed, but there is a greater proportion of Oriental individuals with increased activity. This increased COMT activity results in larger amounts of 3-*O*-methyldopa being produced, and probably explains the substantially lower doses of levodopa used in Orientals compared with Caucasians and the more frequent development of dyskinesia in Filipinos than in Caucasians (Rivera-Calimlim & Reilly 1984). As Chinese, Filipinos and Thais all appear to have a higher frequency of the increased COMT activity, similar findings would be expected in those populations.

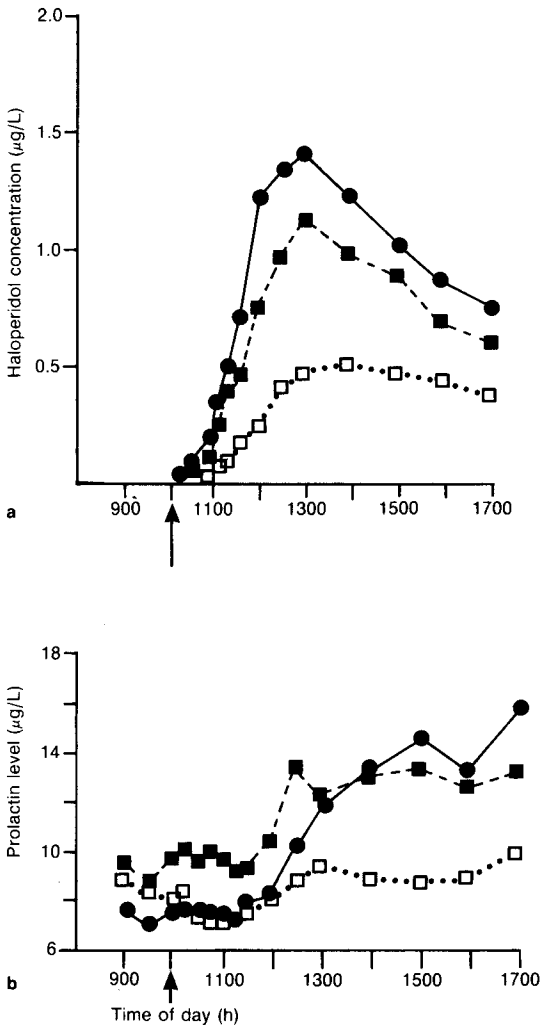

Fig. 8. (**a**) Serum haloperidol concentrations after an oral dose of haloperidol 1mg in 12 Caucasians (□), 11 American-born Asians (■) and 11 Asians born elsewhere (●). (**b**) Serum prolactin levels after the same dose; ↑ = time of dose (from Lin et al. 1988b, with permission).

Table VI. Dose of neuroleptics (chlorpromazine equivalents) required in Asian and White patients (data from Lin & Finder 1983)

	Dose (mg/day)			
	Asian patients		White patients	
	mean	ws	mean	ws
Maximum	849	1066	2081	2205
At discharge	652	827	1456	1568

Abbreviations: ws = weight standardised, i.e. converted to 68kg bodyweight.

3.7 Analgesic Drugs

Although paracetamol (acetaminophen) is principally metabolised by primary conjugation to glucuronides and sulphates, microsomal oxidation followed by glutathione conjugation also occurs (Cummings et al. 1967). Mucklow et al. (1980) compared the elimination of paracetamol in a group of 76 White and 38 Asian immigrant London factory and office workers. The mean paracetamol clearance was 21% less in Asians than in Whites. The explanation for this difference was unclear; however, the use of alcohol, tobacco and oral contraceptives was greater in the White subjects, while the diets of the 2 groups were substantially different as many of the Asian subjects were lactovegetarians. Thus, the relative contribution of environmental factors and genetic factors to racial differences in paracetamol clearance could not be defined. In a group of healthy subjects from Scotland and Ghana, the proportion of paracetamol excreted as mercapturic acid and cysteine conjugates was significantly less in the Ghanaians (Critchley et al. 1983). As it is the oxidation pathway which

produces the hepatotoxic metabolites that are detoxified to the mercapturic acid and cysteine conjugates, the reduced excretion of these conjugates in Ghanaians might imply that that racial group is at less risk of hepatotoxicity from paracetamol.

Codeine, a widely used analgesic drug, is metabolised mainly by conjugation with glucuronic acid. Yue et al. (1989) compared the 8h urine excretion of codeine and its metabolites in 149 healthy Swedish Caucasians and 133 healthy Chinese volunteers after a single oral dose of codeine 25mg. The excretion of unchanged drug was higher in the Chinese group (7.2%) than in the Caucasians (4.3%). The latter excreted significantly greater proportions of codeine-6-glucuronide (62 *vs* 44%). The results suggested that Chinese are less able to metabolise codeine, especially by glucuronidation, which may partially be responsible for the smaller recommended dose in the treatment of pain in Chinese patients.

Zhou et al. (1990f) have recently compared the pharmacodynamics of morphine in Chinese and White subjects. They measured the morphine-induced reversal of the respiration-stimulating effects of CO_2 rebreathing, and also evaluated the alteration of blood pressure and the occurrence of gastrointestinal side effects. The CO_2–ventilatory response curves were significantly depressed following morphine in all subjects. However, the increase in resting partial pressure of CO_2 (pCO_2) and the decrease in expiratory gas flow at pCO_2 = 55mm Hg ($\dot{V}_{E,55}$) were greater in White subjects than in Chinese. The slope of the CO_2–ventilatory response curves was decreased more in Whites, and a greater reduction was observed in blood pressure. The data indicated that White patients have a greater response to morphine than Chinese patients. However, in contrast to the cardiovascular and respiratory effects, the gastrointestinal side effects (vomiting and nausea) occurred in 88% (7 of 8) of the Chinese subjects but none of the Caucasians, implying that Whites were less sensitive to these effects.

4. Conclusions

Ethnic differences in drug response have been a relatively neglected area of investigation. In spite of the well recognised interindividual variability in drug responsiveness and the recently recognised interethnic pharmacokinetic and pharmacodynamic differences, most drugs are still prescribed in similar doses in different ethnic groups.

For polymorphically metabolised drugs, interethnic differences may sometimes be explicable on the basis of an altered frequency of the different phenotypes in different ethnic groups. Examples would include drugs metabolised by acetylation or by the isozymes responsible for oxidation of debrisoquine and mephenytoin. In both of these cases there are marked interethnic differences in the frequency of the 2 phenotypes. In some cases the altered response in different ethnic groups appears to be mediated by some well recognised physiological differences, such as the lower plasma renin levels in Blacks compared with Whites and hence their altered response to β-blockers versus diuretics. For other drugs, however, the explanation for the interethnic differences has not yet been defined. Further studies are required to elucidate both the extent and the aetiology of interethnic differences; in the meantime, physicians must be more circumspect before simply extrapolating the customary dose for a drug in, for example, a US Caucasian population, to individuals worldwide.

Acknowledgements

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