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A comparison of drug protein binding and α_1-acid glycoprotein concentration in Chinese and Caucasians

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α_1-acid glycoprotein (AAG) concentration and the binding of both lignocaine and warfarin were compared in 15 healthy Chinese and age and sex matched Irish (Caucasian) subjects. Both the extent of lignocaine binding and AAG concentrations were significantly ($P < 0.05$) lower in Chinese subjects. No difference was shown in warfarin binding. These results suggest that the binding of basic drugs may be significantly less in Chinese than Caucasians, and lower concentrations of the binding protein AAG are a major determinant of this difference.

Keywords drug binding α_1-acid glycoprotein Chinese Caucasians

Introduction

Much of our knowledge concerning drugs has been gained in only one or two ethnic groups. Indeed many studies do not describe the ethnic or racial background of their subjects and despite these limitations, the findings are often applied to other ethnic or racial groups.

The importance of genetic factors in controlling the disposition of drugs is increasingly appreciated largely in relation to drug acetylation and hydroxylation (Clark, 1985).

Inter-ethnic differences in drug response have recently been recognised. The dosage of propranolol prescribed in China is substantially lower than that widely used in the United States and Europe. The Chinese have a twofold greater sensitivity to the β-adrenoceptor blocking effects of propranolol in part associated with a decreased plasma binding (Zhou *et al.*, 1989). The purpose of this study was to determine the generality of this finding in relation to drug binding. We also examined the concentration of α_1-acid glycoprotein (AAG), the major plasma protein responsible for the binding of basic drugs such as propranolol and lignocaine.

Methods

Two groups of 15 age and sex matched (six female) healthy volunteers participated; one Chinese aged 20 to 27 years and one white Caucasians (Irish) aged 19 to 26 years. All subjects were non-smokers and drug free (including oral contraceptive steroids) with no history of alcohol abuse. The subjects (medical students) lived in a similar environment and all ate a Western diet with the exception that Chinese students (resident in Ireland, mean 5 years) had rice on average four times weekly as opposed to twice for Irish students. Samples were drawn at the same time of day (morning) and at the same season (late Spring/early Summer).

Blood (10 ml) was collected by venepuncture into glass tubes and centrifuged. Serum protein binding was determined at 37° C by an equilibrium dialysis technique using semi-macrocells (Dianorm ®, 1 ml) and a semi-permeable membrane with a molecular weight cut off of 10,000 (Medicell International Ltd). Plasma was separated by the membrane from a similar volume of Na_2HPO_4/KH_2PO_4 buffer, pH 7.45 containing drug (> 98% radiochemically pure). pH stability was achieved as previously described (Brørs & Jacobsen, 1985).[14] C-radiolabelled drug (Amersham) was added to produce a concentration of 0.9 μg ml^{-1} for lignocaine and 2 μg ml^{-1} for warfarin. After equilibration for 4 h 500 μl aliquots were taken from both chambers and radioactivity was determined in a liquid scintillation counter. The percentage of unbound drug was calculated as a ratio of absolute disintegration rates in buffer and plasma.

AAG was measured by radial immunodiffusion (ICL Scientific). Statistical analysis was by the Wilcoxon rank sum test and results are expressed as mean ± s.e. mean. All samples were measured in duplicate with a coefficient of variation of less than 5%.

Results

The results are shown in Table 1.

The binding of lignocaine was significantly less ($P < 0.05$) in Chinese as was AAG concentration. There was no difference in the free fraction of warfarin between Chinese and Caucasian subjects.

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Table 1 Protein binding (expressed as % free) of warfarin and lignocaine and AAG concentration in Chinese and Irish subjects (mean ± s.e. mean; $*P < 0.05$)

	Warfarin (% free)	*Lignocaine* (% free)	*AAG* (gl^{-1})
Chinese ($n = 15$)	1.3 ± 0.1	47.1 ± 1.5*	0.66 ± 0.03*
Irish ($n = 15$)	1.3 ± 0.1	39.6 ± 0.9	0.74 ± 0.04

Discussion

These results show a clear difference in the binding of lignocaine between Chinese and Irish subjects. The reduced binding may be largely attributable to lower circulating concentrations of AAG, the major binding protein for basic drugs. These results are consonant with earlier findings in relation to reduced binding of propranolol (Zhou *et al.*, 1989) in Chinese. Data available (Zhou *et al.*, 1990) since the completion of our study report a similar reduction in the binding of disopyramide. Analysis of the binding isotherm showed reduced binding capacity with no change in binding affinity, in keeping with the suggested explanation of a reduced AAG concentration. Taken together these studies suggest reduced binding of basic drugs in Chinese and emphasise the need for further studies in ethnic groups. As lignocaine toxicity is more closely related to free than to total plasma concentrations (Pieper *et al.*, 1980) such differences may have therapeutic significance.

Furthermore, reduced binding may in part explain the increased sensitivity to propranolol (Zhou *et al.*, 1989) and an increased volume of distribution of diphenhydramine (Spector *et al.*, 1980) in Chinese. Our finding of similar binding of warfarin and other studies which also examined diazepam and salicylic acid binding (Ghoneim *et al.*, 1981; Zhou *et al.*, 1990), suggest that this inter-ethnic difference does not extend to acidic drugs that are primarily bound to either sites I or II on albumin.

A large number of basic drugs including antiarrhythmics, antidepressants, opiates and β-adrenoceptor blockers are primarily bound by AAG (Routledge, 1986). AAG concentration shows a wide variation in health and disease. Age, gender and environmental rather than genetic factors largely determine the variance in the healthy British population. By using a well defined healthy young population living under similar conditions studied at the same time we have minimised environmental influences. While it is possible that presently unidentified factors may be contributory we believe the data support a racial difference in AAG concentration.

Although racial differences in the mydriatic response to cocaine and ephedrine were noted over 60 years ago (Chen & Poth, 1929) differences in sensitivity to alcohol (Wolff, 1972) and more recently to propranolol (Zhou *et al.*, 1989) have also been shown. It is important that in future such studies and kinetic studies in general evaluate the possible contribution of differences in drug binding when considering inter-ethnic differences.

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