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Ethnic differences in nifedipine kinetics: comparisons between Nigerians, Caucasians and South Asians

A. SOWUNMI[1], T. J. RASHID[2], O. O. AKINYINKA[2] & A. G. RENWICK[2]
[1]Department of Pharmacology & Therapeutics, College of Medicine, University of Ibadan, Nigeria and
[2]Clinical Pharmacology Group, University of Southampton, Southampton, UK

Nifedipine was administered to 12 healthy Nigerian volunteers as a single oral dose of 20 mg capsule under fasting conditions. The pharmacokinetic results were compared with published data using the same protocol and analytical method for 27 Caucasians and 30 South Asians. The area under the plasma concentration–time curve (AUC) of nifedipine in Nigerians (808 ± 250 ng ml^{-1} h) was significantly higher ($P < 0.001$) than that in Caucasians (323 ± 116 ng ml^{-1} h) and the difference remained significant ($P < 0.001$) when corrected for body weight. The elimination half-life was also significantly higher ($P < 0.01$) in Nigerians (5.03 ± 1.96 h) than in Caucasians (2.78 ± 1.11 h). No significant differences were observed between Nigerians and South Asians in either AUC or half-life of nifedipine. The AUC of the nitropyridine metabolite was higher ($P < 0.01$) in Nigerians (220 ± 51 ng ml^{-1} h) compared with that in Caucasians (154 ± 56 ng ml^{-1} h) but the difference was not maintained when corrected for body weight. The AUC corrected for body weight and the elimination half-life of the metabolite were significantly higher in South Asians compared with those of Nigerians and Caucasians. The pharmacokinetics of oral nifedipine in Nigerians were similar to those in South Asians and therefore may also arise from a lower systemic clearance compared with Caucasians as has been reported previously for South Asians.

Keywords nifedipine ethnic-differences CYP3A enzymes South Asians Nigerians Caucasians

Introduction

Inter-ethnic differences are important sources of inter-individual variations in drug responsiveness. A number of studies have investigated drug metabolism in black subjects of African origin [1–5]. In addition to the differences in drug metabolism between Caucasians (white) and Africans (blacks) there are also differences in drug response. Most populations are heterogeneous with respect to both environmental and genetic factors that influence drug disposition. Different rates of metabolism may result from variations in genetic constitution; for example the incidence of poor metabolizers of drugs such as debrisoquine and sparteine, which are metabolized by cytochrome P450 2D6 (CYP2D6), varies in populations of different ethnic origin [1–7]. The incidence of slow acetylators is 55–62% in Caucasians, 49% in Nigerians and 13% in Chinese [8].

Metabolism of nifedipine involves initial oxidation to the nitropyridine metabolite by a specific cytochrome P450, CYP3A [9] an enzyme present in the liver and small intestine [10]. The further metabolism of the pyridine metabolite to the carboxylic acid analogue is mediated by a different CYP isozyme [11]. Nifedipine shows a high plasma clearance, which is primarily attributed to extensive hepatic extraction and metabolism [12].

The AUC and half-life of nifedipine were both reported to be significantly higher in a Mexican population [13] and in South Asians [14] compared with Caucasians. The haemodynamic responses persisted for longer in South Asians compared with Caucasians [14] and it was suggested that the differences may have arisen from decreased clearance or increased bioavailability. A subsequent oral/i.v. study [15] showed that the difference arose from a lower systemic clearance in South Asians suggesting that South Asians have reduced

Correspondence: Dr A. G. Renwick, Clinical Pharmacology Group, University of Southampton, Biomedical Sciences Building, Bassett Crescent East, Southampton SO16 7PX, UK

hepatic CYP3A activity compared with that of Caucasians.

Nifedipine has been reported to be particularly effective as an anti-hypertensive agent in low renin hypertension among black hypertensive patients [16]. Calcium channel blockers appear to be as effective as diuretic therapy in hypertensive blacks; they are also proven to be effective adjunct therapy to diuretics for hypertension in blacks [17]. The increased recognition of genetically determined differences in drug metabolizing ability has focused attention on the importance of individualizing drug dose to account for ethnic differences. The aim of the present study was to investigate the pharmacokinetics of orally administered nifedipine in a group of healthy Nigerians and to determine if there are inter-ethnic differences between Caucasians, Nigerians and South Asians.

Methods

Volunteers

The study was approved by the Joint Ethics Committee of the University of Ibadan/University College Hospital and healthy volunteers participated after giving their written informed consent. The clinical aspect of the study was carried out in the University College Hospital, Ibadan, Nigeria after routine biochemical and haematological screening of the subjects and used a protocol identical to that of our previous study in Caucasians and South Asians [14]. None of the subjects was on any regular medication. Some of them occasionally consumed kola nut and alcohol but refrained from these practices during the study period.

Experimental design

Twelve healthy male Nigerian volunteers took part in the study with six from each of the main ethnic groups, i.e. the Yoruba (from South West Nigeria) and Igbo (from South East Nigeria). Their ages ranged from 17 to 40 years, weights from 36 to 62 kg and heights from 1.55 to 1.82 m. Subjects fasted overnight, and on the morning of the study day a cannula was inserted into a forearm vein and a pre-dose blood sample taken. Each subject was given 20 mg of the capsule formulation of nifedipine (Adalat, Bayer UK Ltd, Newbury, UK) with water. The subjects remained in a supine recumbent posture and continued to fast for 3 h after the dose. Venous blood was collected into heparinized tubes at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h after the dose. In addition 12 h and 24 h samples were collected by separate venepuncture. The plasma was separated by centrifugation and processing performed under sodium lamp to prevent photodecomposition. The plasma samples were transferred to glass tubes supplied by the Clinical Pharmacology Group, Southampton and stored at $-20°$ C until transported to the UK in light proof boxes filled with dry ice and then preserved at $-20°$ C until analysis as in our previous study [14]. Pulse and blood pressure were recorded prior to the dose and then prior to each blood sample.

Analytical methods

The samples were analysed in duplicate for nifedipine and the nitropyridine metabolite in the Clinical Pharmacology Group, Southampton by the same reverse phase h.p.l.c. method [18] that had been used for previous studies [12, 14, 15, 18, 20]. The samples of one of the 12 volunteers showed interference during the chromatography and the data had to be excluded from the analysis. The C_{max} and t_{max} are the observed values. Pharmacokinetic parameters were calculated by standard non-compartmental techniques [19] as in our previous study [14]. The elimination half-life was determined by least squares regression analysis applied to the post-peak, log-linear part of the plasma concentration–time curve. The AUC values for both nifedipine and its metabolite were calculated by the trapezoidal rule and extrapolated to infinity by dividing the last measurable plasma concentration by the terminal slope. The observed AUC accounted for an average of 90.0, 95.0 and 91.1% of the AUC to infinity for Nigerian, Caucasian and South Asian subjects respectively. The data of the Nigerians were compared with values for Caucasians and South Asians given the same dose [14]. The results are expressed as mean $\pm$ s.d. and statistical significance was determined by the Mann–Whitney U/Wilcoxon rank sum test and the level of significance was taken as $P<0.05$ using a two-tailed test.

Results

Plasma concentrations of nifedipine in Nigerians were similar to those reported [14] in South Asians and significantly higher than in Caucasians (Figure 1). The C_{max} was not significantly different between the three ethnic groups, but t_{max} was significantly longer in the Nigerians (Table 1) compared with Caucasians ($P<0.05$) and South Asians ($P<0.05$). The AUC of nifedipine was significantly ($P<0.001$) higher in Nigerians (808 ± 250 ng ml^{-1} h) than in Caucasians (323 ± 116 ng ml^{-1} h; 95% CI for difference 335–632 ng ml^{-1} h) and was similar to that in South Asians (802 ± 343 ng ml^{-1} h). Because of the significant differences in body weights (Table 1), the AUC data were adjusted to 70 kg (AUC $\times$ body wt/70) but this did not alter the statistical significance of the large differences found (95% CI for difference 167–389 ng ml^{-1} h). The elimination half-life was significantly prolonged in Nigerians (5.03 ± 1.96 h) compared with Caucasians (2.78 ± 1.11 h; 95% CI for difference 0.83–3.74 h, $P<0.001$). The AUC of nifedipine in the Yoruba (796 ± 249 ng ml^{-1} h) and Igbo (822 ± 277 ng ml^{-1} h) groups were similar and there were no significant differences in any pharmacokinetic parameter.

The C_{max} of the nitropyridine metabolite showed no inter-ethnic differences but the t_{max} was significantly

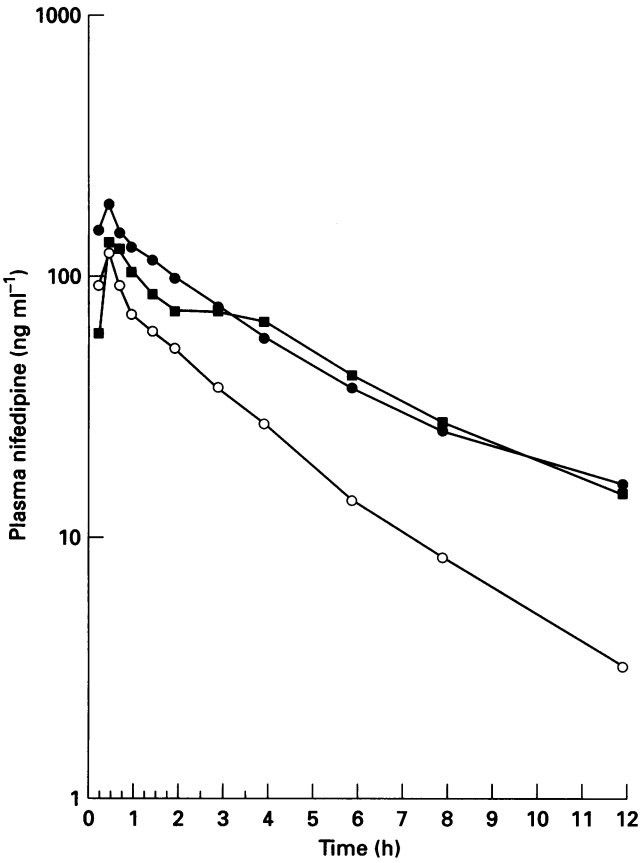

Figure 1 Mean plasma concentrations of nifedipine following a single oral dose (20 mg) given to Caucasians (open circles), Nigerians (filled squares) and South Asians (filled circles) after an overnight fast. Data for Caucasians and South Asians adapted from [14]. The concentrations were statistically significantly different between Caucasians and Nigerian subjects from 3 h post-dosing and between Caucasians and South Asians from 1 h post-dosing. There were no statistically significant differences between Nigerians and South Asians.

prolonged in Nigerians compared with Caucasians ($P<0.05$) and South Asians ($P<0.05$). The AUC of the metabolite (Table 1) was significantly higher in Nigerians than in Caucasians ($P<0.01$) but this difference was removed when the data were normalized for body weight. Adjustment of the AUC of the metabolite for body weight gave a significant difference between Nigerians and South Asians. The elimination half-life was similar in Caucasians and Nigerians but longer in South Asians. The ratio of the C_{max} of nifedipine to that of its metabolite was significantly higher in Nigerians than in Caucasians ($P<0.05$). The ratio of the AUC of nifedipine to that of its metabolite was also significantly higher in Nigerians compared with Caucasians ($P<0.01$).

In Nigerians the pulse rate was increased significantly compared with predose values from 0.5 h after the dosing until 3 h after the dose. The systolic and diastolic blood pressure were both reduced significantly from 0.25 h after the dose until 8 h after dosing compared with predose values. Pharmacokinetic–pharmacodynamic modelling of the individual or mean data did not give meaningful estimates; the maximum observed changes in heart rate (+15 beats min^{-1}) and diastolic blood pressure (−13 mmHg) were similar to those reported in South Asians given 20 mg as capsules [14].

Discussion

The significantly prolonged t_{max} of nifedipine in Nigerians ($P<0.01$) compared with that of both Caucasians and South Asians suggests delayed gastric emptying or prolonged absorption of the drug. Slower gastric emptying is associated with a decrease in C_{max} and AUC for nifedipine [20] and therefore if the difference in t_{max} was to have affected the data in this study it would have been to underestimate the difference between Nigerians and Caucasians that would have been found if both groups had shown a similar t_{max}. The underlying mechanism for the differences in AUC and half-life between Nigerians and Caucasians is not known and could be genetic, dietary or environmental.

The increased AUC of nifedipine in Nigerians could be due to higher bioavailability and/or reduced systemic clearance. The increased AUC in South Asians compared with Caucasians has been shown to be due to a lower systemic clearance rather than a difference in bioavailability [15], which suggested that the hepatic CYP3A4 enzyme involved in the metabolism of nifedipine may be expressed in South Asians at a lower level than in Caucasians or alternatively a lower CYP3A activity may have arisen from an environmental influence. The pharmacokinetics of oral nifedipine in Nigerians were similar to South Asians and it is possible that the differences with Caucasians have a similar cause. CYP3A isoenzymes are found in both the liver and the intestinal wall [21, 22] and the differences described in this paper may arise from differences in the *in vivo* activity of CYP3A4 or CYP3A5 in the liver or intestine. The systemic clearance of nifedipine approaches that of high clearance drugs in Caucasians but a decrease in hepatic enzyme activity, as suggested for South Asians [15] and possibly Nigerians, would mean that it was not a high clearance drug in these populations. In the Nigerians the mean AUC corrected for body weight was 1.8 times that in Caucasians and the half-life was also 1.8-fold greater than in Caucasians and therefore a simple difference in systemic clearance would explain both the higher AUC and prolonged half-life of nifedipine.

Differences in plasma protein binding are unlikely to be involved in the higher plasma concentrations of nifedipine in Nigerians and South Asians, since increased plasma protein binding would cause both higher peak plasma concentrations due to a decrease in the apparent volume of distribution but a shorter half-life because clearance would be largely unaffected [23]. The pharmacokinetic data in Nigerians and South Asians showed both a higher AUC and increased half-life compared with the data for Caucasians suggesting that differences in protein binding are unlikely to be the cause of the kinetic differences. The percentage protein binding of nifedipine has been reported to be similar in South Asians and Caucasians [14]. Dihydropyridines increase

Table 1 Ethnic differences in the pharmacokinetics of nifedipine following a single oral dose of 20 mg as capsules

Parameter	*Nigerians*	*Caucasians*[a]	*South Asians*[a,b]
Number studied	11	27	30
Body weight (kg)	54±8***†††	73±7	64±5***
Nifedipine			
C_{max} (ng ml^{-1})	205±149	172±107	241±162
t_{max} (h)	0.75 (0.5–4.0)*†	0.5 (0.25–0.75)	0.5 (0.25–1.5)
AUC (ng ml^{-1} h); mean	808±250***	323±116	802±343***
AUC (ng ml^{-1} h); median	811 (617–1030)***	281 (220–396)	775 (594–932)***
Normalised AUC (ng ml^{-1} h)[c]	605±155***	334±119	737±326***
Half-life (h)	5.03±1.96**	2.78±1.11	6.54±3.38***
Nitropyridine metabolite			
C_{max} (ng ml^{-1})	54±28	68±33	71±37
t_{max} (h)	2.0 (0.5–4.0)*†	0.5 (0.25–1.5)	0.5 (0.25–1.5)
AUC (ng ml^{-1} h); mean	220±51**	154±56	292±113***
AUC (ng ml^{-1} h); median	214 (189–233)**	151 (112–169)	256 (205–366)***
Normalised AUC (ng ml^{-1} h)[c]	168±52††	160±59	266±100***
Half-life (h)	4.16±2.21†	3.39±1.69	8.14±5.48***
Ratio nifedipine/metabolite			
C_{max}	3.43±1.15*	2.61±1.12	3.29±1.53*
AUC	3.86±1.47**	2.29±1.13	2.87±1.41

[a]data from [14].

[b]$n=27$ for metabolite data.

[c]AUC corrected for body weight (AUC × body weight/70).

The results are the means±s.d. and/or medians with inter-quantile range in parentheses.

*$=P<0.05$; **$=P<0.01$; ***$=P<0.001$ compared with Caucasians,

†$=P<0.05$; ††$=P<0.01$; †††$=P<0.001$ compared with South Asians by Mann–Whitney U/Wilkcoxon rank sum test.

hepatic blood flow [24–26] and the differences between ethnic groups might have arisen from a difference in the hepatic blood flow response to the dose administered. An increase in hepatic blood flow could decrease first-pass metabolism of nifedipine but by increasing the systemic clearance this would prevent an increase in the AUC and would also result in a shorter half-life. Therefore, the increase in AUC and half-life of nifedipine in both Nigerians and South Asians suggests lower activities of the metabolizing enzymes rather than altered hepatic blood flow.

The AUC of the nitropyridine metabolite in Nigerian subjects was not significantly different from the Caucasian data when normalized for body weight, but was significantly lower than the results for South Asians, which suggests that there could be a difference between Nigerians and South Asians in the further metabolism of the nitropyridine metabolite (assuming a similar extent of formation during first pass metabolism). The higher ratio of both C_{max} and AUC of nifedipine to its metabolite in Nigerians compared with that of Caucasians was due to the higher C_{max} and AUC values of the parent compound rather than lower values for the metabolite. The differences in half-life and AUC of the metabolite corrected for body weight between South Asians and Nigerians suggest a possible minor difference in the activity of the P450 isozyme involved in the metabolism of the pyridine metabolite.

Previous studies on drug metabolism in Nigerian subjects have focused on the population distribution of pathways showing polymorphism in other ethnic groups for example acetylation [27, 28], debrisoquine oxidation [29, 30] and metoprolol oxidation [30] and the metabolism and pharmacokinetics of drugs used in the treatment of malaria [31, 32] and leprosy [33]. Interesting previous observations of possible relevance to the results in the present paper are the higher plasma concentrations of quinidine [34] but not chloroquine [32] in Nigerian subjects compared with Caucasians, the increase in the median ratios for urinary free debrisoquine or metoprolol to their respective hydroxy metabolites in Nigerian populations [30] and the unusually low levels of oxidative metabolites of ethinyl-oestradiol in the urine of Nigerian women given a dose of radiolabelled mestranol [35].

The inter-ethnic differences reported for nifedipine in this study could be relevant to other substrates of CYP3A4 in Nigerians and may have important therapeutic implications. In contrast to these findings with nifedipine, cyclosporine which is also a substrate for CYP3A4, shows no significant difference in systemic clearance but a significantly lower bioavailability in black Americans compared with whites [25]: therefore the ethnic difference reported in this paper may not be universally applicable to all CYP3A4 substrates and/or all patient groups of African descent.

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