Original Articles

ETHNIC DIFFERENCES IN NIFEDIPINE PHARMACOKINETICS AND PHARMACODYNAMICS: COMPARISON OF MIDDLE EASTERN ARABS WITH OTHER POPULATIONS

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تم دراسة حركية دواء النفيديبين وتأثيره الدوائي على خمسة ذكور عرب أصحاء حيث قورنت نتائجهم بالنتائج المنشورة والخاصة بالأعراق الأخرى . وقد تلقى كل شخص جرعة فموية (٢ × ١٠ مغ) في حالة الصيام، وتم تقدير تراكيز الدواء في البلازما بطريقة نوعية من طرق كروماتوغرافيا السوائل عالية الكفاءة . كما تم قياس معدل دقات القلب وضغط الدم الانقباضي والانبساطي . وقد تم تقدير نصف العمر الحيوي، وأقصى تركيز للدواء في البلازما، وزمن أقصى تركيز، وتبين أنها ٢٠ر٣ ± ٢١ر٠ ساعة، و ٢٣٠ر٤ ± ٣٦ر٤ نغ/مل، و ٩٥ر٠ ± ٢٣ر٠ ساعة، على التوالي . أما متوسط زمن البقاء في الجسم، والتصفية الكلية للدواء من الجسم فكانتا ٨٢ر٣ ± ٧٦ر٠ ساعة، و ٣٠ر٠ ± ٠٦ر٠ ل/ ساعة.كغ، على التوالي . وكانت تراكيز الدواء في العرب مماثلة لتلك الخاصة بالجنوب آسيويين، واليابانيين، والنيجيريين، ولكنها كانت أعلى معنوياً من تلك الخاصة بالقوقازيين (الأشخاص من ذوي العرق الأبيض) . كما كانت المساحتان تحت المنحنى، العادية والمعدلة، أعلى في العرب بمقدار ٨ر٢ و ٤ر٣ مرات من مثيلتيهما لدى القوقازيين . أما التأثيرات الدموية للنيفيديبين فكانت متشابهة في كل الأعراق التي تم دراستها . وتستنتج الدراسة أن الجرعة الخاصة بالعرب يجب أن تكون أقل من الجرعة المخصصة للقوقازيين .

The pharmacokinetics and pharmacodynamic effects of oral nifedipine were studied in five healthy male Middle Eastern Arab subjects and their results were compared with those reported for other populations. Each subject received a single 2×10-mg dose under fasting conditions and plasma concentrations were determined by a specific HPLC method. Heart rate and systolic and diastolic blood pressure were also monitored. The elimination half-life, maximum plasma concentration and time to maximum plasma concentration were found to be 3.20±0.21 h, 230.4±36.4 ng/ml and 0.95±0.23 h, respectively. Mean residence time (**MRT**) and operative clearance (**CL/F**) were determined to be 3.82±0.67 h and 0.30±0.06 L/h.kg, respectively. Plasma concentrations in Middle Eastern Arab subjects were similar to those reported for South Asians, Japanese and Nigerians, but they were significantly higher than in Caucasians. The **AUC** and normalized **AUC** were 2.8 and 3.4 folds greater in Middle Eastern Arab subjects than in Caucasians. The hemodynamic effects of nifedipine were comparable in all ethnic groups studied. In conclusion, Middle Eastern Arab patients should be initiated with a lower dose than would be administered to Caucasians.

Keywords: Nifedipine, ethnic differences, pharmacokinetics, pharmacodynamics

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Introduction

Nifedipine is a dihydropyridine calcium channel blocker used extensively in the treatment of hypertension, vasospastic and exercise-induced angina pectoris and other cardiovascular diseases (1,2). Following oral administration, the drug undergoes first-pass metabolism predominantly through initial oxidation to the nitrodipine analogue dehydronifidipine by a specific cytochrome P-450, CYP3A4 (3,4), an enzyme found in the liver and small intestine (5). This inactive oxidation product is further metabolized by a different cytochrome isozyme to the carboxylic acid metabolites, which are excreted in urine (6,7).

The interethnic variability in the frequency of the poor metabolizer phenotype in different populations with respect to the metabolism of a wide variety of drugs is well-documented (8). It was found that the frequency of poor metabolizers of debrisoquine-type hydroxylation in Saudi Arabians and Egyptians ranged from 1% to 1.4% (9,10), whereas it was less than 1% in Chinese (11) and Japanese (12) subjects. On the other hand, the frequency of poor metabolizers of debrisoquine-type hydroxylation was about 10% in Caucasian subjects.

Kleinbloesem and co-workers (13) observed a wide interindividual variability in the plasma kinetics of nifedipine. The frequency distribution of its area under the plasma concentration-time curve (AUC) has been shown to be bimodal. Consequently, they proposed the existence of two distinct phenotypes of nifedipine metabolizers that can be grouped as fast and slow according to AUC resulting from the administration of a 20-mg dose. These results were refuted by two other studies (14,15) where they studied the pharmacokinetics of nifedipine and concluded that, in a large population of 130 healthy subjects, high variability was observed but neither bimodality nor polymorphism was detected. On the other hand, the existence of bimodal distribution of nifedipine metabolizers was supported by Hoyo-vadillo and colleagues (16) where they observed, unlike Caucasians, that slow metabolizers are more frequent in Mexicans. They suggested the occurrence of polymorphism with respect to nifedipine disposition kinetics due to genetic basis. Several other studies have addressed the issue of interethnic differences in nifedipine pharmacokinetic parameters (17-20). Ahsan and co-workers found that AUC was 3 fold higher in South Asians than in Caucasians and $t_{1/2}$ of both nifedipine and nitropyridine were also significantly greater in South Asians than in Caucasians (20). To eliminate the possibility that diet could be the reason for observed variability, consumption of a spicy curry diet for 3 days by Caucasians did not significantly affect the pharmacokinetic parameters of a single oral dose of nifedipine. These results were supported by another study (19) where they reported that the ethnic difference between South Asians and Caucasians could be important in relation to other substrates for CYP3A4. Patients of South Asian origin may require lower doses of nifedipine. The AUC and C_{max} values were also found to be higher in Japanese and Mexican healthy subjects compared to Europeans and North Americans (18). These differences were attributed to the nutritional habits as well as to possible differences in phenotypes of nifedipine metabolizers. The $t_{1/2}$ and AUC of nifedipine in Nigerian population were reported to be significantly higher than that in Caucasians (20) but no significant differences were observed between Nigerians and South Asians in this regard. The discrepancies between all previously reported results could have arisen from differences in doses or formulations (19). The difference in the rate of drug metabolism may be due to differences in genetic constitution and regulation of enzyme activity.

This study was conducted to investigate the pharmacokinetic and pharmacodynamic parameters of nifedipine after a single oral dose in healthy Middle Eastern subjects and compare them to data published for other populations. An extensive review of literature revealed that no reported work has been performed to evaluate the effect of polymorphism in nifedipine metabolism and its implications on drug disposition in Middle Eastern subjects.

Subjects, Materials and Methods

Subjects

The study was conducted in the department of Medicine at King Khalid University Hospital. Five healthy male volunteers ranging in age between 30-46 years (mean ± SD; 36.8 ± 8.0 years), whose mass and height do not deviate more than 10 percent from the values in the Metropolitan Scale (88.6 ± 4.6 kg), participated in this study. The volunteers underwent comprehensive physical examination, medical history, kidney and liver function tests, creatinine, BUN, SGOT, SGPT, glucose, uric acid, total proteins, albumin, lactate dehydrogenase, alkaline phosphatase,

and cholesterol tests. Hematology (complete blood count and differentials) was also performed. Clinical evaluation revealed no history of cardiovascular, renal, hepatic, gastrointestinal or respiratory disorder. No one proved to be allergic to the medications under study. The study was performed according to the recommendations of the declaration of Helsinki. All volunteers were required to give an informed written consent after receiving detailed instructions concerning the study performance, restrictions and possible adverse effects. Copies of the signed and dated consent forms were given to each subject.

Study Plan

Volunteers were not allowed to take any medication 14 days prior to and during the study, or ingest caffeine-containing food or beverages 24 hr prior to the study. In the early morning (7:00 A.M.) of the study day, the volunteers reported to the site of the study at King Khalid University Hospital (KKUH) and their vital signs were checked. An indwelling venous cannula was inserted into an antebrachial vein of the overnight-fasted volunteer, and two blood samples were taken 30 minutes and just before drug administration. A single dose (2×10 mg) of nifedipine capsules was administered. Administration of the drug was followed immediately with the ingestion of 240 ml of water. Blood samples (7 ml) were drawn at 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, 420, 480, 600 and 720 minutes after drug administration. The samples were collected in heparinized tubes and centrifuged immediately. Two aliquots were transferred to labeled plastic tubes wrapped in aluminum foil and stored at -20°C pending nifedipine assay. The sampling was carried out under sodium lamp or extremely subdued light and all tubes and syringes were wrapped in aluminum foil because of the photolability of nifedipine. Food intake during the study period was permitted in the form of standardized meals served before the drug administration and at 5 and 10 hours after drug administration for lunch and supper, respectively. Each volunteer received 240 ml of tap water at 0, 2, 4, 6 and 8 hours after drug administration and 200 ml of orange juice with his meals. Tea was served after 8 hours of drug administration.

The volunteers remained ambulatory and no smoking or strenuous activity was permitted during the study day. After the end of the study, volunteers were subjected to the same medical evaluations outlined before. Pulse rate and blood pressure were recorded prior to drug administration and immediately before each blood sample.

Nifedipine Assay

Nifedipine plasma concentrations were measured using an accurate and specific reversed-phase high performance liquid chromatographic method (HPLC) modified from the method of El-Sayed et al. (21). Plasma (1 ml) was pipetted to a 15-ml glass tube, 500 µl of sodium bicarbonate and 30 µl of the internal standard diazepam (1 µg/ml) was added. The mixture was shaken on a vortex mixer for one minute, extracted with 5 ml of diethylether, and centrifuged for 10 minutes at 3,000 rpm. The organic layer was transferred to a 15-ml glass centrifuge tube and evaporated to dryness under a stream of supplied laboratory air outlet. The samples were reconstituted with 250 µl of the mobile phase, vortex mixed for 20 seconds and transferred to a 1.5 ml Eppendorf tube and centrifuged again for 3 minutes at 13,000 rpm. A 50-µl aliquot was then injected into the loop injector. The HPLC system consisted of a solvent delivery pump Model M45 (Waters Associate, Milford, Mass., USA), a UV variable wavelength detector Model 481, a recorder Model SE120 (BBC, Goerz, Metrawatt). Chromatographic separation was performed using a Novapak C_{18} column (100 mm length × 8 mm i.d.; 4 µm particle size) packed in Waters RCM 8×10. The mobile phase consisted of acetonitrile-water (48:52 v/v) adjusted to pH 4.0 by adding few drops of glacial acetic acid. Mobile phase was degassed every day by passing through a 0.45 µm membrane filter (Millipore, Bedford, MA, USA). The flow rate was adjusted to 1.8 ml/min. The chart speed was fixed at 0.4 cm/min and the effluent was monitored using ultraviolet detection at 240 nm and attenuation at 0.02 a.u.f.s.

The assay for nifedipine in plasma showed overall inter- and intra-assay precision 4.29% and 3.44%, respectively, and a lower limit of quantitation of 10 ng/ml.

Pharmacokinetic Analysis

Nifedipine pharmacokinetic parameters were determined from the plasma concentration-time profiles using WinNonlin computer program (Scientific Consulting, Inc, USA, 1997). The model independent parameters: area under the plasma concentration-time curves up to the last measurable concentration ($\mathbf{AUC}_{0-t}$) and up to time infinity ($\mathbf{AUC}_{0-\infty}$), the maximum plasma concentration ($\mathbf{C}_{max}$), the time to maximum plasma concentration ($\mathbf{T}_{max}$), and the half-

life ($t_{1/2}$) were calculated. The elimination $t_{1/2}$ was computed from the first-order elimination rate, which was estimated by least squares linear regression of the plasma terminal log-linear phase of the log concentration-time curve. AUC_{0-t} was determined by linear trapezoidal method. $AUC_{0-\infty}$ was calculated by adding to AUC_{0-t} the quotient resulting from dividing the last measurable nifedipine plasma concentration by the negative slope of the final log-linear phase of the plasma concentration-time curve.

The mean residence time (**MRT**) was calculated using the following relationship:

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

where $AUMC_{0-\infty}$ is the area under the first moment curve, and calculated by the trapezoidal rule from a plot of the product of nifedipine plasma concentration and time *vs.* time.

The hemodynamic effects (percent changes in systolic and diastolic blood pressures) were correlated to nifedipine plasma concentration by fitting the data to the sigmoidal E_{max} model using the following function and nonlinear regression analysis:

$$E = \frac{E_{max} C^n}{EC_{50} + C^n}$$

where **E** is the hemodynamic effect, EC_{50} is the plasma concentration that corresponds to 50% of the maximal hemodynamic effect (E_{max}), **C** is nifedipine plasma concentration and **n** is the slope factor.

Statistical Analysis

Comparisons of pharmacokinetic parameters between Middle Eastern Arab subjects and other populations were carried out by the Student's t-test for independent samples assuming homoscedastic or heteroscedastic model. The analysis of variance (ANOVA) was performed to provide statistics about the overall significance of the nonlinear regression for the sigmoidal E_{max} model being used. In addition, Durbin-Watson test was used to check for

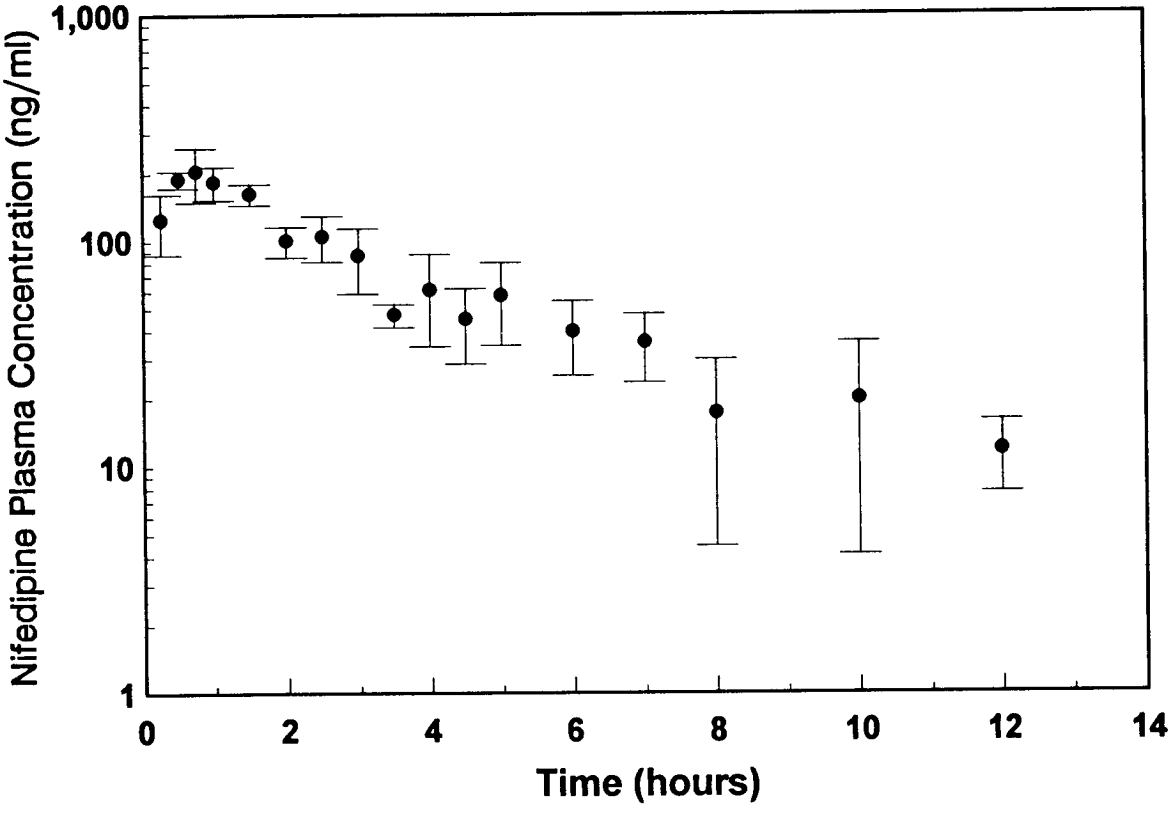

Figure 1. Mean nifedipine plasma concentration-time curves following the oral administration of 2×10 mg capsules in Middle Eastern Arab subjects.

autocorrelation and validity of the model. The results were expressed as mean ± SEM. Differences were considered significant if p was < 0.05.

Results

Nifedipine was well tolerated by all subjects. Figure 1 depicts mean ± SEM plasma nifedipine concentration data for the five subjects studied. Following oral administration of a single 20-mg dose, nifedipine plasma concentration rose, reaching a maximum concentration ($\mathbf{C}_{max}$) of 230.4 ± 36.4 ng/ml in 0.95 ± 0.23 h. The plasma concentration decreased as a function of time with a half-life of 3.2 ± 0.21 h. The plasma concentration at 0.25 h was measurable in only two subjects. Three samples from two subjects underwent hemolysis, therefore, they were discarded and their results were not included in the final analysis of data. The drug was detectable 12 h after the administration of the dose with levels adequately higher than the minimum quantifiable concentration. The pharmacokinetic parameters are given in table 1.

The **MRT** averaged 3.82 ± 0.67 h. The operative volume of distribution at steady state ($\mathbf{V}_{ss}/\mathbf{F}$) was found to be 1.07 ± 0.22 L/kg and the operative total body clearance (**CL/F**) was determined to be 0.30 ± 0.06 L/h.kg.

The minimal effective plasma concentration that produces a significant vasodilation was reported to be 15 ng/ml (22). This therapeutic threshold was reached in all Middle Eastern subjects within the first 30 minutes after the drug administration and was maintained for 9.0 ± 2.91 h (range, 5.5-11.75 h).

The observed maximal reduction in diastolic blood pressure and in systolic blood pressure in Middle Eastern Arab subjects were 15.4% ± 2.0% and 22.1± 5.1%, respectively. Figure 2 shows the mean reductions in diastolic (**–Δ%DBP**) and in systolic (**–Δ% SBP**) blood pressure in Middle Eastern Arab subjects after the administration of a single dose of 2×10 mg capsules of nifedipine. The percent change in **DBP** and **SBP** were fitted by nonlinear regression to sigmoidal $\mathbf{E}_{max}$ model using a slope factor (n) values ranging from 0.5 to 2. The best fit was obtained with n=1 and 1.5,

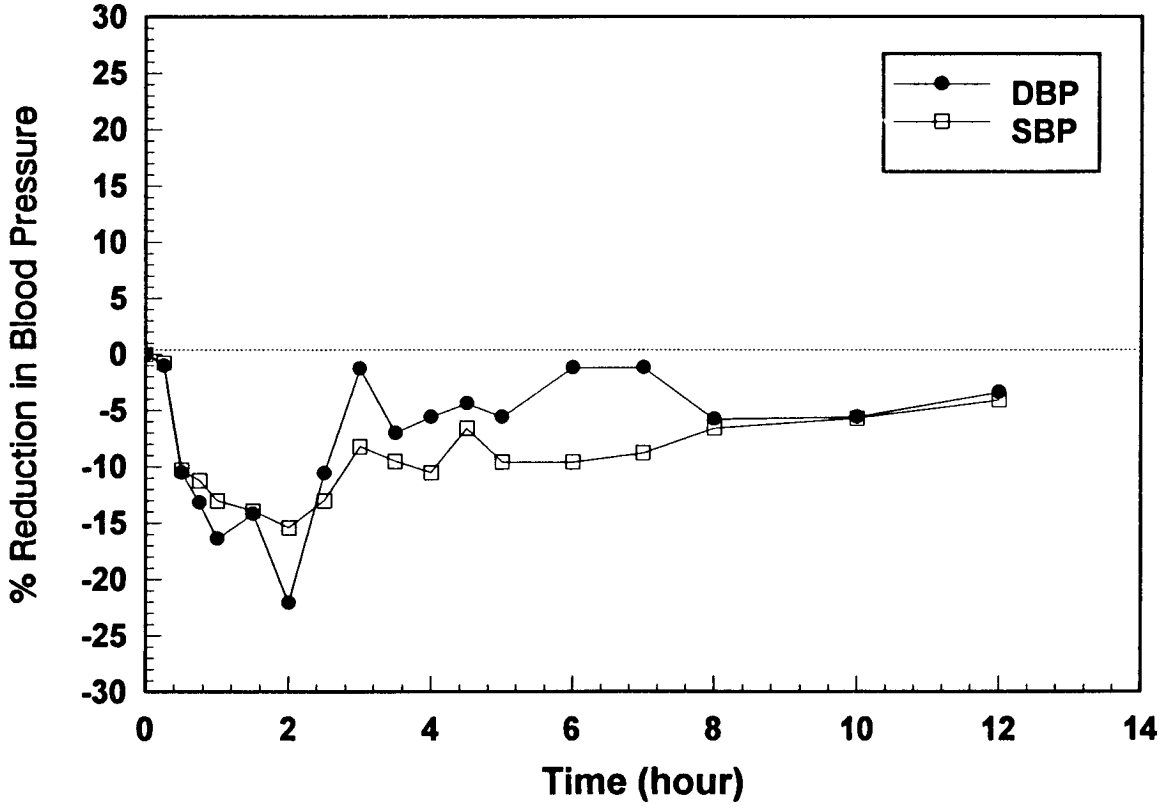

Figure 2. The mean reduction in diastolic blood pressure (**–Δ% DBP**) and in systolic blood pressure (**–Δ% SBP**) following the oral administration of 2×10 mg capsules in Middle Eastern Arab subjects. Error bars were omitted for clarity.

Table 1. Pharmacokinetic parameters (mean±SEM) of nifedipine after the administration of 2×10 mg dose in different populations.

Population	N	Age Range (y)	C_{max} (ng/ml)	t_{max} (h)	$t^{1}/_{2}$ (ng.h/ml)	AUC AUC	Normalized	Ref
Japanese	6	20-25	236±29	1.0±0.4	2.54±0.25	598.0±10	524±8.8*	23
South Asians	30	21-32	241±30	0.9±0.9	6.5±0.62**	802±63	737±58	19
	5	25-32	250±84.5	1.2±0.2	8.3±0.63**	989±74.2	933±70	17
Nigerians	12	17-40	205±45	0.75 (0.5-4.0)[a]	5.03±0.6**	808±75.4	605±46.7	20
Caucasians	27	19-46	172±20.6	0.8±0.15	2.78±0.21	323±22.3*	342±23.6**	19
Middle Eastern	5	30-46	230.4±36.4	0.95±0.23	3.20±0.21	906±220.6	1143±268.4	This study

a. Range

* $p<0.05$ compared with Middle Eastern Arab subjects.

** $p<0.001$ compared with Middle Eastern Arab subjects.

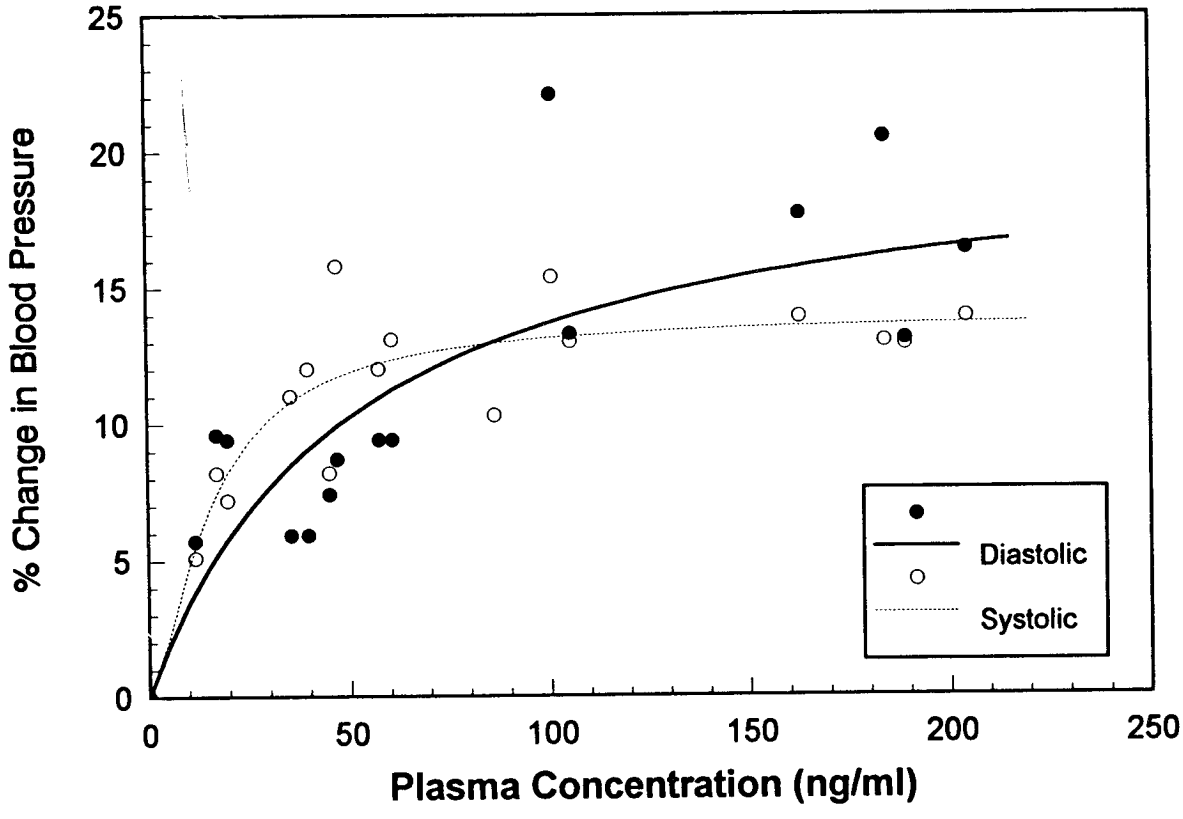

Figure 3. Nonlinear regression fit of the hemodynamic effect (–Δ% **SBP** or (–Δ% **DBP**)) vs. nifedipine plasma concentration in Middle Eastern Arab subjects. (n=1 and 1.5 for DBP and SBP, respectively).

Table 2: Concentration-hemodynamic effect parameters of nifedipine in Middle Eastern Arab subjects following the administration of single oral dose (2×10 mg). Parameters were estimated from fitting data to the sigmoidal E_{max} model with varying slope factors.

n	E_{max}	EC_{50}	D-W[a]	r	p[b]
Systolic BP					
0.5	20.0±3.6	5.6±2.6	1.94	0.88	0.00001
1	13.4±1.7	11.4±7.9	1.93	0.71	0.00099
1.5	**14.0±0.71**	**61.4±19.1**	**2.42**	**0.91**	**0.00001**
2	13.4±0.59	240.7±80.7	2.41	0.91	0.00001
Diastolic BP					
0.5	63.2±47.9	38.3±37.1	1.30	0.90	0.00001
1	**20.7±3.0**	**51.2±19.9**	**1.58**	**0.90**	**0.00003**
1.5	17.2±2.0	220.1±91.3	1.31	0.82	0.00016
2	16.5±1.8	1213.5±586.6	1.02	0.77	0.00038

a. Durbin-Watson test

b. Analysis of variance (ANOVA) for regression.

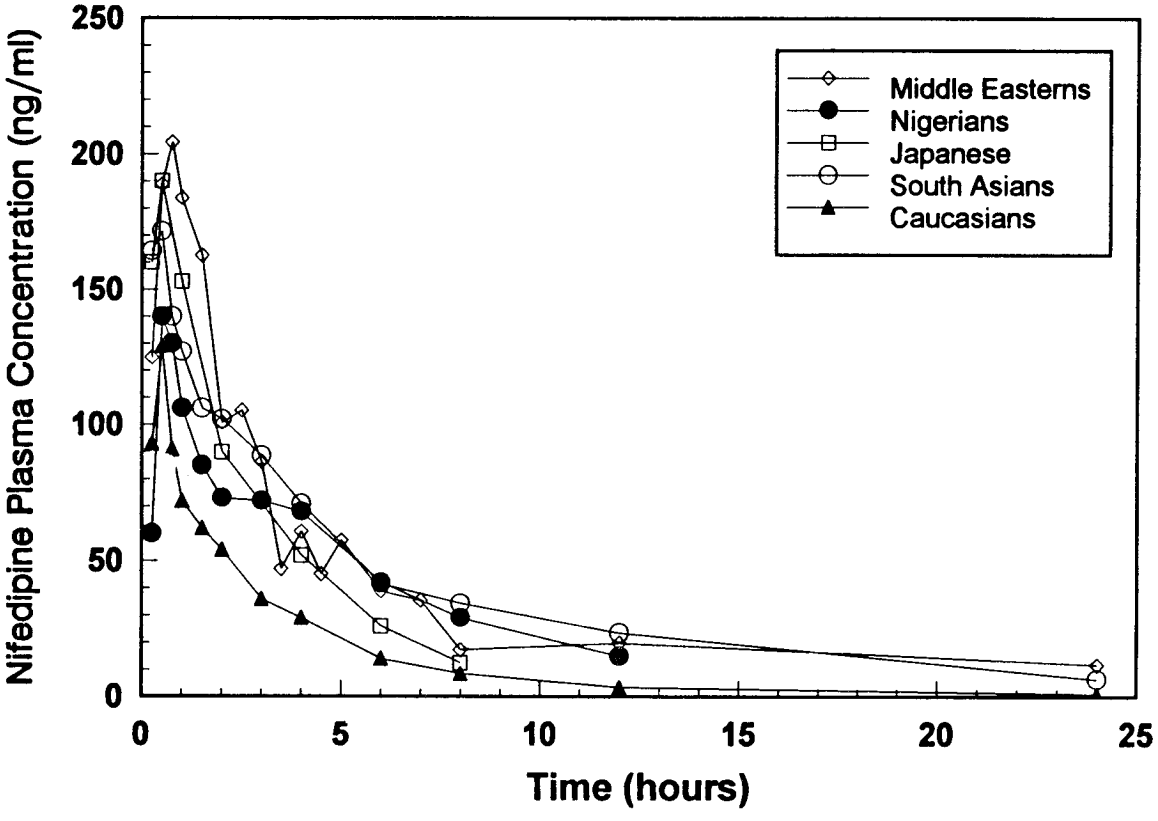

Figure 4. Nifedipine plasma concentrations in Middle Eastern Arabs subjects compared with those in South Asians (Ref. 17,19), Nigerians (Ref. 20), Japanese (Ref. 25) and Caucasians (Ref. 17). Error bars were omitted for clarity.

respectively where the highest coefficient of determination and the highest Durbin-Watson coefficient were obtained (Table 2). Figure 3 depicts the observed percentage reduction in **DBP** and **SBP** as a function of Nifedipine plasma concentration with the fitted lines. The respective E_{max} was found to be 20.7% ± 3.0% and 14.0% ± 0.7% and EC_{max} was found to be 51.2 ± 19.9 ng/ml and 61.4 ± 19.1 ng/ml for **DBP** and **SBP**, respectively.

Discussion

In recent years, attention has been focused on the interethnic differences in drug disposition. Racial variability in pharmacokinetics has been attributed to a multitude of reasons including genetic, environmental and nutritional factors. This area of research has been neglected in the Arab world and the Middle East where few investigators, if any, have ventured in it. The purpose of this study was to determine the pharmacokinetic parameters of oral nifedipine in Middle Eastern Arab subjects and to compare them with those reported for other populations. Reports suggested that some studies were carried out using analytical procedures in which nifedipine was codetermined with its primary metabolite dehydronifedipine leading to inaccurate estimation of pharmacokinetic parameters (18). For this reason, reports in which a specific analytical technique was used were considered.

Two studies evaluated the pharmacokinetics of oral nifedipine (20 mg capsules) in South Asians compared with Caucasians (17,19). In the first study, 5 South Asian subjects were compared with 27 Caucasian subjects (17). In the second study, 30 South Asian subjects were studied and their results were compared with previously reported data for Caucasians (19). Figure 4 depicts a comparison of nifedipine plasma concentrations in Middle Eastern Arabs subjects with those in South Asians, Nigerians, Japanese and Caucasians. As observed by most investigators, the pharmacokinetic profiles of nifedipine after the administration of capsules are characterized by rapid plasma concentration decay due to its fast distribution.

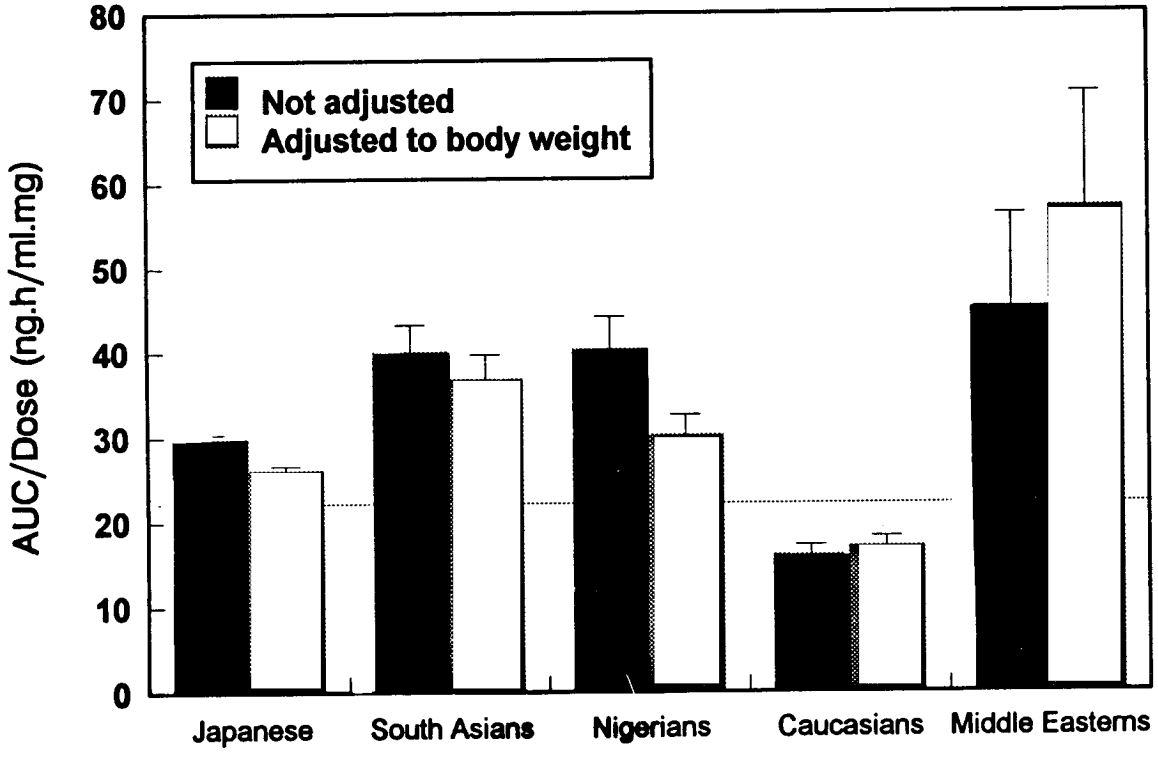

Figure 5. Comparison of dose-normalized area under the curve (**AUC/Dose**) between various ethnic groups.

The plasma concentrations in Middle Eastern Arab subjects were similar to those reported for South Asians (17,19), Japanese (23) and Nigerians (20), but they were significantly higher than in Caucasians (17). There were no significant differences in $\mathbf{C}_{max}$ and $\mathbf{T}_{max}$ between the five ethnic groups except that $\mathbf{T}_{max}$ in Nigerians was significantly longer than in other ethnic groups including Middle Eastern Arabs.

The $\mathbf{t}_{1/2}$ of nifedipine in all populations ranged from 2.54 ± 0.25 h in Japanese subjects to 6.5 ± 0.62 h in South Asian subjects. The $\mathbf{t}_{1/2}$ values in Middle Eastern Arabs, Japanese and Caucasians were similar ($p > 0.05$), but they were significantly longer ($p < 0.05$) in South Asians and Nigerians than in Middle Eastern Arabs. It is very difficult to explain the wide interethnic variability in $\mathbf{t}_{1/2}$. Hoyo-Vadillo et al. (24) emphasized the relevance of the characterization of the distribution phase to obtain accurate estimates of the pharmacokinetic parameters of nifedipine. They stated that the true $\mathbf{t}_{1/2}$ should be longer than 2 h, while Rämsch and Sommer (25) found that the actual $\mathbf{t}_{1/2}$ of nifedipine could be as long as 10 h after i.v. infusion of the drug. These differences in $\mathbf{t}_{1/2}$ estimates between populations can be attributed, in part, to the failure of some analytical techniques used in some studies to determine low concentrations in the terminal elimination phase, as well as to the inadequacy of sampling time. The greater $\mathbf{t}_{1/2}$ of nifedipine in South Asian and Nigerian subjects compared with Caucasians was postulated to be caused by decreased clearance or an increased apparent volume of distribution as a result of decreased protein binding of the drug. This hypothesis has been rejected as a possible cause of longer $\mathbf{t}_{1/2}$ in both populations (19,20).

Although the **AUC** in Middle Eastern Arabs is 12%, 13% and 52% higher than that in South Asians, Nigerians and Japanese subjects, respectively, these differences did not reach statistical significance ($p>0.05$). The high but not statistically significant difference between Middle Eastern Arabs and Japanese subjects in **AUC** may have arisen from the interindividual variability which was augmented by the small sample sizes used in the Japanese study (23) and the present study. Another possible reason for the observed difference in **AUC** between Middle Eastern Arabs and Japanese is the difference in body weight between both groups. Normalization of the **AUC** to 70 kg body weight (**AUC**×body weight/70) revealed that this difference, in fact, is statistically significant ($p<0.05$). On the other hand, **AUC** and normalized **AUC** were 2.8 and 3.4 folds, respectively, greater in Middle Eastern Arab subjects than in Caucasian subjects ($p<0.01$). The most plausible explanation for the slight increase in **AUC** in Middle Eastern Arabs over those reported for South Asians, Nigerians, and the highly significant increase over those reported for Caucasians is that this difference may have resulted from the lower systemic clearance and/or the higher bioavailability of nifedipine in Middle Eastern subjects. The reduced systemic clearance is more likely explanation since no significant differences were observed between Middle Eastern Arabs and Caucasians in $\mathbf{t}_{1/2}$, $\mathbf{C}_{max}$ and $\mathbf{T}_{max}$. Rashid and co-workers (26) have shown that the higher **AUC** values in South Asians compared with Caucasians was due to lower levels of the hepatic **CYP3A4** enzyme. Similar results were observed for Nigerians (20) and South Asians (17,19). These results in South Asians, Nigerians and Middle Eastern Arabs contradict the fact that nifedipine is a high extraction ratio drug and its clearance is mainly determined by hepatic blood flow rather than its intrinsic clearance or enzyme activity. Ahsan et al. (17,19) and Sowunmi et al. (20) suggested that nifedipine, unlike its pharmacokinetic behaviors in Caucasians, might not be a high extraction ratio drug in South Asians and Nigerians after all. The results described in this study for Middle Eastern Arab subjects are in agreement with this hypothesis. Protein binding of nifedipine can be disregarded again as a possible cause of the higher **AUC** values since the increase in protein binding would produce higher $\mathbf{C}_{max}$ due to the decrease in the apparent volume of distribution and consequently the $\mathbf{t}_{1/2}$ would be shorter because the clearance would not be affected.

Kleinbloesem and co-workers (27) studied the pharmacokinetics of nifedipine in Dutch volunteers who received two 10-mg capsules of the drug. They proposed the existence of two distinct phenotypes, designated as fast and slow, of nifedipine metabolizers that can be identified by **AUC** value after oral administration. Subjects with **AUC** >450 ng.h/ml were considered slow metabolizers of the drug, whereas subjects with **AUC**<450 ng.h/ml were considered fast metabolizers. The range of **AUC** values observed in our study was 487.0-1760.7 ng.h/ml indicating that all subjects studied were extremely slow metabolizers according to this criterion. Whether these results can be generalized to all Middle Eastern subjects or not is a matter that warrant further investigation using a larger

representative sample of the population. To account for dose difference between studies, **AUC** was normalized to dose. Subjects with **AUC/Dose** ratio higher or lower than 22.5 ng.h/ml.mg were labeled slow or fast metabolizers, respectively. Figure 5 depicts a comparison of this ratio between various ethnic groups. It can be observed that this ratio is slightly higher in Middle Eastern Arab subjects than in South Asian and Nigerian subjects, but it is about 1.5 and 3 folds higher in Middle Eastern Arab subjects than in Japanese and Caucasian subjects, respectively.

The hemodynamic effects of nifedipine (**–Δ% DBP**) in Middle Eastern Arab subjects were comparable with those reported for South Asians (19) ($\mathbf{C}_{max}$=15% and $\mathbf{EC}_{50}$=60 ng/ml) and Nigerians (20), but they were significantly different from those reported by Kleinbloesem and co-workers (27) ($\mathbf{EC}_{50}$=22.4±3.2 ng/ml).

In conclusion, this study demonstrates the existence of interethnic differences between Middle Eastern Arabs and Caucasians. The study has shown that Middle Eastern Arab subjects are more likely to be slow metabolizers of nifedipine like South Asians and Nigerians, consequently, the doses designed for Caucasians might not be appropriate for them and dose reduction should be instituted.

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