Biochemical Pharmacology, Vol. 33, No. 22, pp. 3721–3724, 1984.
Printed in Great Britain.

0006-2952/84 $3.00 + 0.00

VARIABILITY IN NIFEDIPINE PHARMACOKINETICS AND DYNAMICS: A NEW OXIDATION POLYMORPHISM IN MAN

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(received: 17 August 1984; accepted: 28 August 1984)

INTRODUCTION

Since wide individual variability has been observed in the disposition kinetics of nifedipine (1, 2), a study was undertaken in a larger number of subjects to analyze frequency distributions of kinetic and dynamic parameters following a single oral dose of nifedipine. The drug is extensively metabolized into inactive metabolites, the first step being oxidation of the dihydropyridine nucleus to a pyridine moiety. Subsequently the ester moiety is hydrolyzed (formation of urinary metabolite, M-I) and further metabolism takes place by hydroxylation of the 3-methyl group (formation of urinary metabolite, M-II) (3). The rate of metabolism is relatively rapid, as estimated by a systemic plasma clearance of approximately 500 ml/min (2,3). The drug undergoes substantial first-pass metabolism, which was shown to vary between 10 and 70 % (2). Since a close correlation between plasma concentration and haemodynamic effects has been demonstrated (2,4), large variability in drug disposition could implicate large variability in clinical effects.

MATERIALS AND METHODS

Fifty-three healthy subjects (33 males, 20 females), aged 26.8±8.6 yrs (range 18–54 yr) participated after giving informed consent. The protocol was approved by the Ethical Committee of the hospital. Hepatic, renal and cardiovascular diseases were excluded by medical history, physical examination and by appropriate laboratory tests. Volunteers had not taken any medication for at least 3 weeks before the study, except for contraceptive steroids in 12 females. During the course of the study all subjects refrained from alcohol and caffeine-containing beverages. The experiments started at 8.30 a.m. after an overnight fast. An indwelling canula with a heparin lock was inserted for blood sampling into an anticubital vein. After 15 min of recumbency basal heart rate (HR) and blood pressure (BP) were measured. Nifedipine was administered orally in capsules (total dose 20 mg) and was ingested with 100 ml water. Blood samples were drawn in heparinized tubes just prior to drug administration and at 15,30, 45 min 1,1.5,2,3,4,6 and 8 h. BP and HR were measured at the same times. Urine was collected by spontaneous micturation from 0–8 and 9–24 h after drug administration. Plasma nifedipine concentrations and M-I concentrations were measured by HPLC (5).
Areas under the plasma concentration time curve (AUC) were calculated by trapezoidal rule and elimination half-life by least-squares regression analysis after log transformation. Intrinsic clearance was calculated by dividing the dose by AUC, assuming complete absorption. Clearance for production of M-I ($CL_{\rightarrow M\text{-}I}$) was calculated according to:

$$CL_{\rightarrow M\text{-}I} = CL_{intrinsic} \times \% \text{ of Dose excreted in 24 hours urine.}$$

Frequency distributions of AUC, 8 h urinary excretion, Δ% HR at 1–2 h after dosing, and Δ% HR at 5–6 h after dosing were constructed and probit transformations were performed. Statistical analysis was performed by Wilcoxon's two-tailed rank order test. In order to check the reproducibility of the data, the study was repeated in 8 subjects of whom 5 exhibited relatively rapid and 3 relatively slow metabolism. The interval between the two experiments was at least 4 weeks.

RESULTS

The distribution of AUC and 8 h urinary excretion of M-I for the 53 volunteers are shown in the form of histograms in Fig. Ia and Ib respectively. The shape of the graphs was bimodal. This was further supported by the probit lines (Fig. Ia and Ib). Other relevant kinetic parameters are listed in table I.

With regard to the effects on HR, a unimodel distribution was found at 1–2 h after dosing, but a clear bimodal distribution was obtained at 5–6 h after drug administration (Fig. II). All subjects with an AUC > 450 ng.h/ml (chatched bars), belonged to the group with the largest effect on HR at 5–6

Table I. Pharmacokinetic and pharmacodynamic data of nifedipine in 53 healthy subjects (mean ± S.D.).

	$t_{1/2el}$ (h)	$Cl_{\rightarrow M-I}$ (l/min)	Urinary excretion (24 h) (%)	DBP_{1-2h} (Δ%)	DBP_{5-6h} (Δ%)
Slow metabolizers (AUC ≧ 450 ng.h/ml)	2.4±0.8	0.2±0.1	47.1±6.3	-15.8±3.0	-7.0±5.8
Rapid metabolizers (AUC < 450 ng.h/ml)	2.2±0.7	0.9±0.4	63.1±7.4	-13.2±4.3	-1.8±3.9
P-value	N.S.	p < 0.001	p < 0.01	N.S.	p < 0.01

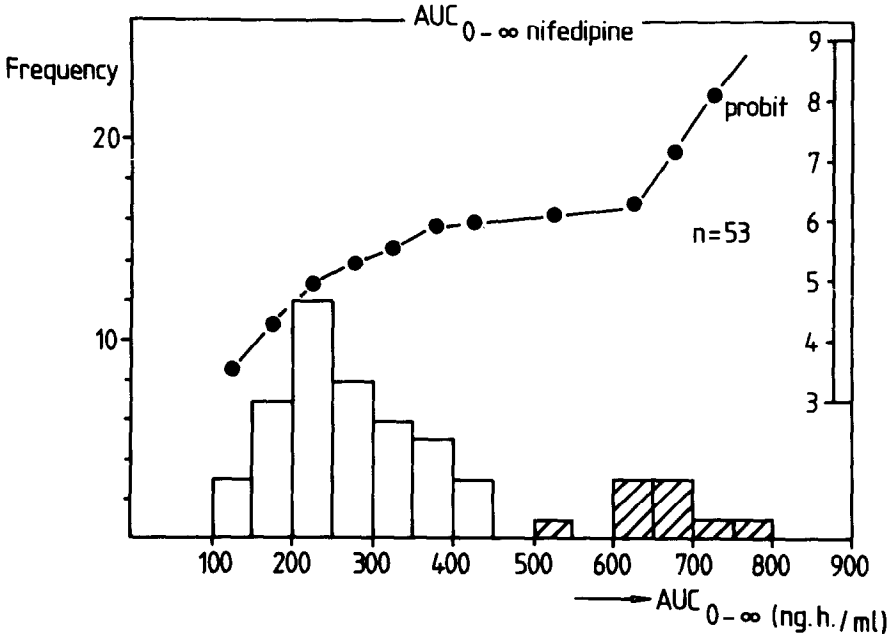

Figure 1a. Frequency histogram and probit line of AUC of nifedipine in plasma after oral administration to 53 healthy subjects.

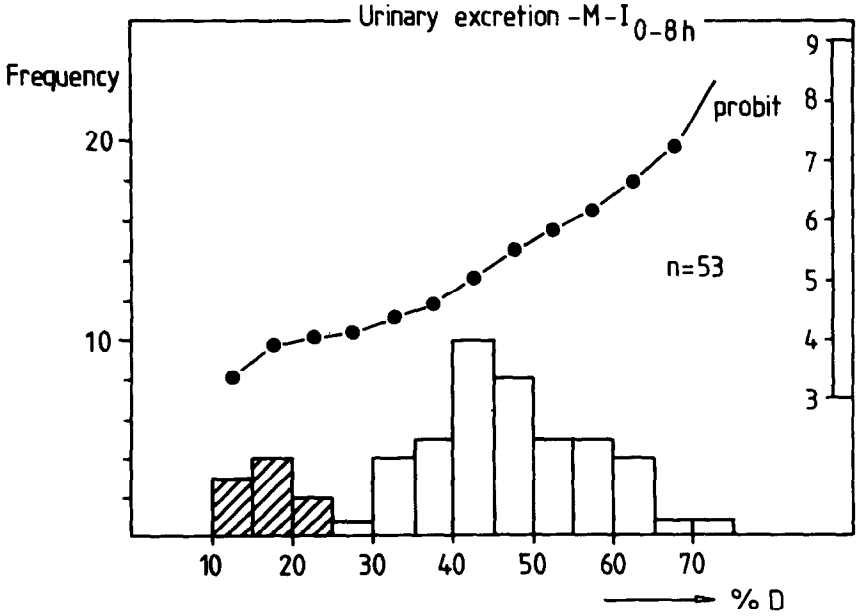

Figure 1b. Frequency histogram and probit line of 8 h urinary excretion of M-I following oral administration to 53 healthy subjects.

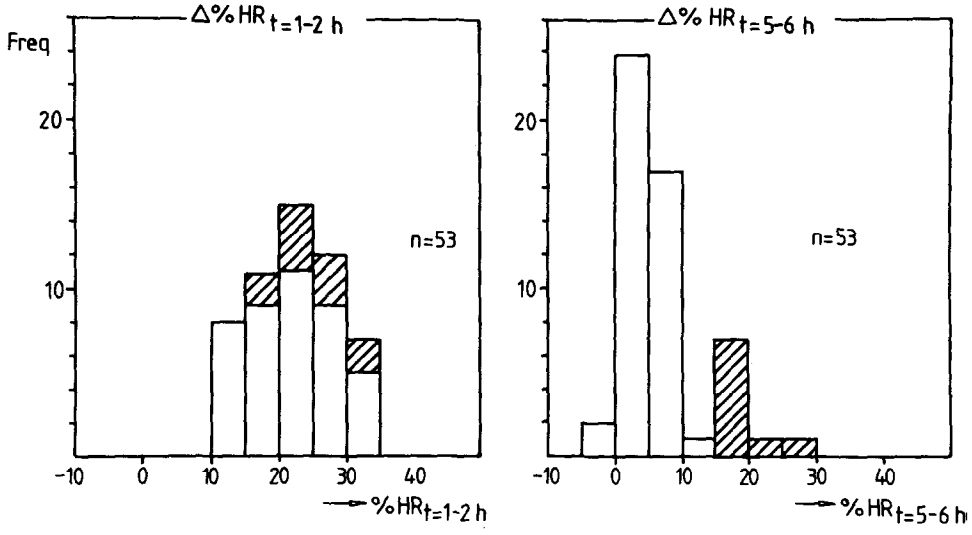

Figure II. Frequency histogram of changes in heart rate (Δ %HR) at t = 1-2 h and 5-6 h after oral administration of nifedipine to 53 healthy subjects.

h, whereas at 1-2 h they were evenly distributed (see Fig.II). Effects on DBP 1-2 and 5-6 h after dosing are listed in table I. The two modes did not differ significantly with regard to age, gender, smoking habits, and the use of oral contraceptives. From repeated studies in 8 subjects it appeared that the intraindividual variation in AUC was less than 25% in relatively rapid metabolizers (AUC < 450 ng.h/ml), whereas it was less than 10% in the other group. There were no shifts from one mode to the other.

DISCUSSION

The present data confirm the previous observations that the disposition of nifedipine is highly variable. However the bimodal frequency distribution of the AUC clearly suggests that polymorphism exists with respect to disposition kinetics of nifedipine. Thus two phenotypes exist; the principal (44/53; 83%) characterised 25-70% urinary M-I excretion in 8 h and AUC < 500 ng.h/ml and the minor (9/53; 17%) characterised < 25 % urinary M-I excretion in 8h and AUC > 500 ng.h/ml.
Assuming complete absorption in all subjects (3), the differences in AUC are primarily determined by differences in the extent of first-pass metabolism, since nifedipine is a high clearance drug. Therefore its elimination half-life depends much on liver blood flow and consequently no differences in half-life were found between relatively fast and slow metabolizers. Data on urinary excretion during 8 h after dosing are in accordance with bimodality, but differences were less when the 24 h excretion was considered. This indicates that rate rather than extent of M-I formation is affected in slow metabolizers, which is clearly expressed in the differences in $Cl_{5-6\ h}^{M-I}$.

Bimodality was also found for haemodynamic effects (HR and DBP) at 5-6 h after dosing, whereas distribution at 1-2 h was unimodal. This can be explained on the basis of a sigmoidal concentration-effect relationship, which we have found previously (2,4). At 5-6 h after drug administration nifedipine plasma concentrations are still in the steep part of the concentration-effect curve in slow metabolizers, whereas with fast metabolizers these have already returned to the flat part of the curve. Although also at 1-2 h after dosing plasma concentrations were higher in slow metabolizers, the maximal effects were already achieved in all subjects. A practical consequence of these findings would be that in slow metabolizers the duration rather than intensity of the (side) effects is influenced, which could have implications for dosing schedules. We have reported elsewhere that dissociation of the blood pressure lowering effect of nifedipine and tachycardia is possible when controlling drug input at a relatively slow rate (2,4). This knowledge could in principle be applied to protect the slow metabolizer from disturbing tachycardia.

It has been shown for several drugs that metabolic polymorphism has a genetic basis (6,7). Further studies including in families are now underway, to determine whether or not polymorphism of nifedipine is also under genetic control. Preliminary experiments did not show a correlation between nifedipine kinetics and the metabolism of sparteine or debrisoquine (Dr J.R.Idle personal communication). It is likely that, if the bimodality of the rate of nifedipine metabolism is indeed genetically determined, this would represent a new oxidation polymorphism. The present findings could also have consequences for other drugs containing the dihydropyridine moiety, e.g. several other Ca-channel blockers, since the same metabolic pathway is involved.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. J.R. Idle, Department of Biochemical Pharmacology, St. Mary's Hospital, London for very constructive advice and Mrs. H.C.N. Kappelle-de Vries for typing the manuscript. The study was supported in part by a grant from Bayer A.G. (Wuppertal, FRG).

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