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LACK OF BIMODALITY IN NIFEDIPINE PLASMA KINETICS IN A LARGE POPULATION OF HEALTHY SUBJECTS

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Introduction

Wide interindividual variability has been observed in the plasma kinetics of nifedipine (NF) and the frequency distribution of its area under the plasma concentration-time curve (AUC) has previously been shown to be bimodal in a population of 53 healthy subjects [1]. NF seems to be oxidized by the cytochrome P-450 system [2] and first-pass metabolism was found to vary between 10 and 70 % [3]. After oral administration, aromatization leads to the formation of a pyridine moiety M-0, the major first-pass metabolite [4]. Studies with human liver microsomes have indicated that M-0 is formed via oxidation by the P-450 system [2].

In the present study the disposition of NF was assessed in 130 newly recruited healthy young Dutch subjects, after administration of 20 mg NF as slow release tablet together with sparteine and phenytoin in a cocktail study design [5,6]. The aim was to study the reproducibility of the observed bimodality in plasma kinetics, because in another recent population study with NF in 172 healthy subjects in which only urinary excretion of the acid metabolite M-I (main metabolite in urine) was assessed, no bimodality in the frequency distribution histogram was observed [6], in contrast to the first population study [1].

Materials and methods

In this study 130 healthy subjects participated (69 males, 61 females), aged 23.0 ± 2.9 yrs (range 19-33), after having given their written informed consent. The protocol was approved of by the Ethics Committee of the Leiden University Hospital. All were healthy according to clinical history, physical examination and routine blood analysis. All subjects were non medicated, except for oral contraceptives in 24 females. Thirty-seven were smokers defined as >3 cigarettes/day. After an overnight fast a cocktail was administered of 20 mg NF as slow release tablet, 50 mg sparteine (as sparteine sulphate) and 100 mg phenytoin sodium. Thirteen blood samples were taken between 0 and 32 h via an indwelling cannula or by venapunction. Concentrations of NF and M-0 were determined by HPLC [7](modification to be published) and GC-ECD (modified from [8]). Areas under the plasma concentration-time curves (AUC) were determined by applying the linear logarithmic trapezoidal method. Frequency distributions of AUC of NF, AUC of M-0 and of their ratio were constructed and these distributions were tested for normality by means of the chi-square test. Pearson correlation coefficients between pharmacokinetic parameters were calculated. Only data of NF and M-0 are reported in this communication.

Results

The frequency distribution of AUC of NF, AUC of M-0 and of their ratio are shown in Fig. 1-3. AUC distribution of NF and M-0 are both highly skewed (chi-square test for normality: $p<0.001$), but no clear bimodality can be observed. Distribution of AUC NF/AUC M-0 is also highly skewed and seems to exhibit bimodality: a number of 4 observations (ratio >5) form a

distict group. The hatched bars illustrate that the magnitude of these 4 ratios was due to a low AUC of M-0, rather than to a high AUC of NF (Fig. 1-3). Relevant kinetic data are listed in Table 1. AUC of NF varied almost tenfold, AUC of M-0 seventeenfold and AUC NF/AUC M-0 fifteenfold. Correlation coefficients between parameters of Table 1 were calculated (Table 2). The strongest correlation was found between AUC of NF and AUC of M-0 (0.62).

Table 1 Pharmacokinetic data of nifedipine (NF) and its pyridine metabolite M-0 in 130 healthy subjects, after intake of 20 mg NF as slow release tablet.

			mean	SD	range	P
NF	AUC	(ng·h/ml)	314	155	105 - 1010	<0.001
	Cmax	(ng/ml)	37.9	16.1	12.4 - 110	0.002
M-0	AUC	(ng·h/ml)	177	114	51 - 887	<0.001
	Cmax	(ng/ml)	25.9	12.1	9.0 - 88.2	0.001
Ratio	AUC NF/AUC M-0		2.0	1.0	0.4 - 5.8	<0.001

AUC= area under plasma concentration-time curve; Cmax= maximum plasma concentration; SD= standard deviation; P= probability of normality as tested by chi-square test.

Table 2 Pearson correlation coefficients between pharmacokinetic parameters of nifedipine (NF) and its pyridine metabolite M-0.

	Cmax NF	AUC M-0	Cmax M-0	Ratio AUC NF/AUC M-0
AUC NF	0.52	0.62	0.29	0.28
Cmax NF		0.19	0.36	0.23
AUC M-0			0.59	-0.38
Cmax M-0				-0.41

AUC= area under plasma concentration-time curve; Cmax= maximum plasma concentration; All correlation coefficients were significant at $p < 0.03$ level.

Discussion

The present data illustrate that the frequency distribution of the AUC of NF, after oral administration of a 20 mg slow release tablet to a large population of healthy subjects, is highly skewed, but not bimodal and therefore not subject to a detectable polymorphism. It is clear that NF disposition after oral administration is highly variable and this observation as such may be of clinical importance. The present study differed markedly from the first population study by Kleinbloesem et al. [1], with regard to sample size, dosage form and applied cocktail approach. Sample size is of major importance, because a false-positive bimodality is less likely, when the number of observations increases. Also application of probit-analysis may lead to a false-positive interpretation of bimodality [9]. The slow release preparation, in comparison with the capsules in the first population study, may have

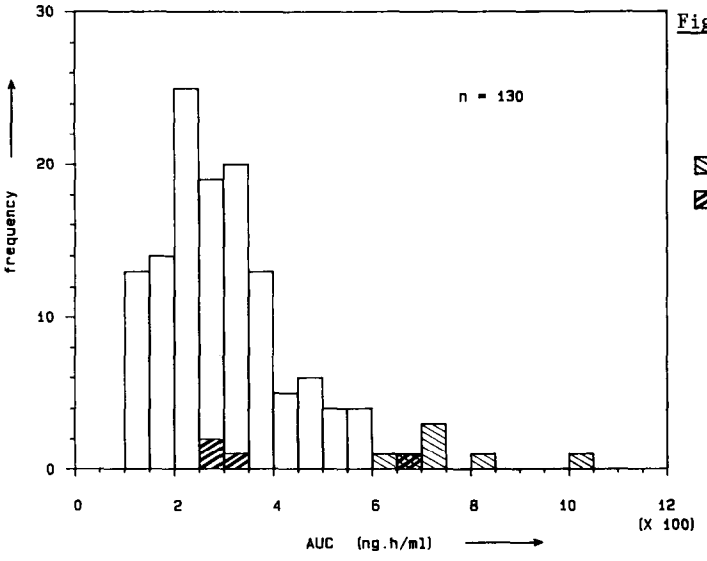

Fig 1 Frequency distribution of AUC of nifedipine in plasma after oral administration of 20 mg as slow release tablet.
▨ 7 subjects with highest AUC NF.
▨ 4 subjects with highest ratio AUC NF/M-0.

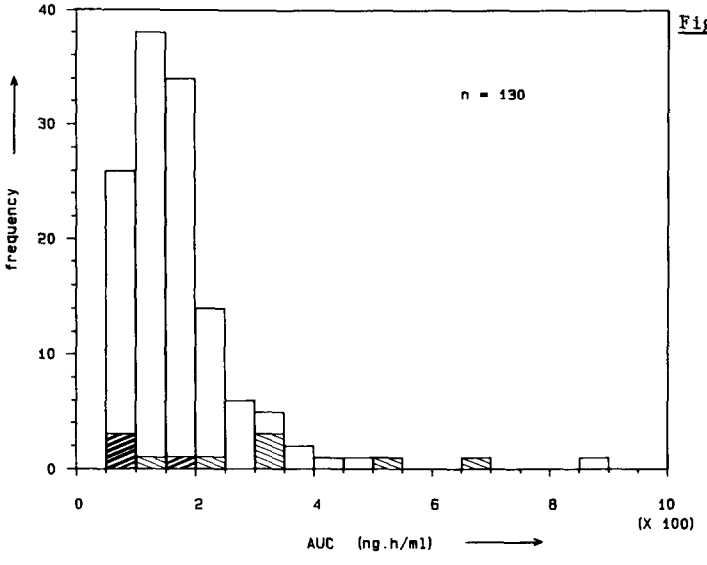

Fig 2 Frequency distribution of AUC of pyridine metabolite M-0. (Hatching same as in Fig 1.)

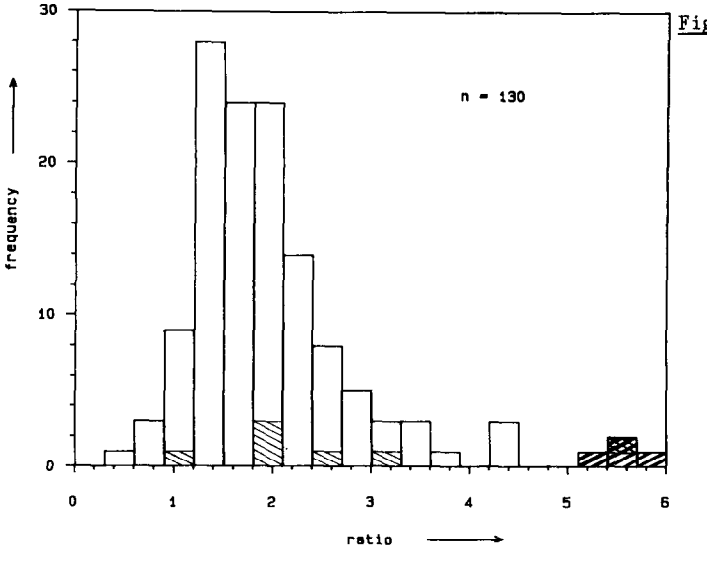

Fig 3 Frequency distribution of the ratio AUC NF/AUC M-0. (Hatching same as in Fig 1.)

influenced the difference in outcome, however regarding the even higher variability in the present study it is unlikely that this would obscure bimodality.

NF was administered simultaneously with sparteine and phenytoin. Prior to this population study an interaction study was carried out in eight subjects, in which no significant effect of the other probe drugs on the disposition of NF was observed (to be published). Thus, the cocktail approach can be ruled out as a major factor confusing a possible bimodality.

The plasma kinetics of the major first-pass metabolite M-O was also investigated (Fig. 2, Table 1), in contrast to the previous studies [1,6]. The AUC of M-O was highly variable, but no impairment in formation of M-O could be detected, which is not in agreement with the findings of Schmid et al. [10]. A relatively strong positive correlation was found between the AUC of NF and the AUC of M-O (table 2), which is not to be expected if impairment in M-O formation during first-pass leads to a high AUC of NF. The hatched bars in Fig. 1 and 2 represent the 7 subjects with highest AUC of NF and their corresponding AUC of M-O. Their location in Fig. 2 illustrates that a high AUC of NF is not accompanied by a low AUC of M-O.

The ratio of AUC NF/AUC M-O seems to exhibit bimodality, regarding the 4 subjects with a ratio >5. Interestingly, only one of them was characterized by a high AUC of NF and all 4 had a very low AUC of M-O. From the present data it cannot be differentiated whether the low AUC of M-O was a result of reduced formation or increased elimination kinetics. Insufficient information on M-O disposition per se is available, hence polymorphism via this route cannot be completely excluded so far. Clinical importance of variability in M-O disposition is however limited, because this metabolite seems to be pharmacologically inactive [11].

It can be concluded that in a large population of healthy subjects high variability but no bimodality, i.e. detectable polymorphism, in overall NF disposition was observed. Most likely limited sample size has led to the accidental observation of bimodality in the study by Kleinbloesem et al. [1]. It can as yet not be ruled out however that single metabolic pathways other than M-O formation exhibit polymorphism.

After completion of the present investigation we became aware of another population study with nifedipine in 59 healthy subjects, in which no bimodality in AUC was observed either (A.G. Renwick et al., personal communication).

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