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Accumulation of nifedipine after multiple doses

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The single and multiple dose pharmacokinetics of oral nifedipine capsules, 10 mg, have been examined in five patients with peripheral vasospasm. After a single dose, nifedipine was rapidly absorbed in three and slowly absorbed in two patients. Mean bioavailability parameters included a t_{max} of 2·9 h, a C_{max} of 33·3 ng ml^{-1} and a $AUC_{0-8\,h}$ of 113·3 ng h ml^{-1}. After multiple dosing with either 10 or 20 mg every 8 h for 10 days the mean t_{max} at steady state was 2·1 h while the mean dose-corrected (to 10 mg) C_{max} and $AUC_{0-8\,h}$ were 51·9 ng ml^{-1} and 146·9 ng h ml^{-1}, respectively. The mean elimination rate constant was 0·173 h^{-1} after both single and multiple doses. The mean extent of accumulation of nifedipine, defined as the ratio of $AUC_{0-8\,h}$ (steady state)/$AUC_{0-8\,h}$ (single dose), was 1·3; we concluded that nifedipine accumulates in the body when it is administered every 8 h. This should be taken into account when predicting steady state serum concentrations and haemodynamic effects of nifedipine from single dose kinetic data.

Nifedipine, a calcium channel-blocking agent typically administered in multiple doses, has a mean elimination half-life in normal volunteers, following the administration of a single, 10 mg, oral dose, of 3·4 to 8 h (Foster et al 1983; Raemsch & Sommer 1983). From these figures significant accumulation of nifedipine dosed 3 or 4 times a day would be expected. However, there do not seem to be any reports including pharmacokinetic data obtained following its repeated administration that could substantiate its accumulation characteristics. Raemsch & Sommer (1983) found no accumulation or any changes in its pharmacokinetics after administering 10 mg three times daily for one week to normal volunteers.

Recently we were able to study the pharmacokinetics of nifedipine after single oral dose and multiple oral doses to a group of patients who were part of an experimental protocol to evaluate the effectiveness of nifedipine in ameliorating peripheral vasospasm. Because of the scarcity of data relating to the steady state pharmacokinetics of the drug it was thought that the study would provide insight into the accumulation characteristics of nifedipine.

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Materials and methods

Five patients (3 males, 2 females) were involved; they were aged 21–31 years (mean 23·6 yrs) and non-obese with a mean body weight of 56·5 ± 4·9 kg. Renal and hepatic function tests were within normal limits. The patients gave informed consent and they were hospitalized for the duration of the study. Because pain and other symptoms were part of their disorder, various medications, including flurazepam, hydroxyzine, indomethacin and pethidine (meperidine) were permitted during the study. One patient was receiving phenytoin. We confirmed that these medications did not interfere with the assay for nifedipine and that they had not been previously reported in the literature to alter the disposition of nifedipine. But pethidine has been reported to inhibit gastric emptying and to delay the rate, but not the extent, of absorption of paracetamol (Nimmo et al 1975), however, the patients had access to the drug as needed and the daily dose throughout was essentially unchanged.

On the first day a single, 10 mg, oral dose of nifedipine (Procardia, Pfizer Inc., New York) was administered to each patient after at least 2 h without food. Blood (5 ml) was obtained predose and at 0·5, 1·0, 2·0, 3·0, 4·0, 5·0, 6·0, 7·0 and 8·0 h post dose. Blood pressure and pulse were monitored at each sampling time. Serum was collected from the blood samples and frozen at −20 °C for future nifedipine analysis. All blood and serum samples were protected from light.

After the response to the single dose was evaluated, nifedipine, 10 mg every 8 h, was taken by the patients for the next 5 days. At this point, based on the individual responses to the drug, the dose was continued or increased to a maximum of 60 mg per day. Four of the five patients were able to tolerate 20 mg, and the fifth 10 mg every 8 h. These doses were continued for 5 days

to achieve a steady state. On the tenth day of the study, after the second dose of nifedipine, blood samples were collected at times identical to those following the single dose.

Nifedipine in serum was determined by gas chromatography with electron capture (Lesko et al 1983) and concentrations were derived from a standard curve of peak height ratio (nifedipine/internal standard) versus concentration which was rectilinear from 5 to 100 ng ml^{-1}. The sensitivity of the assay with a signal-to-noise ratio of 3:1 was 5 ng ml^{-1} and the precision, as relative standard deviation, at this concentration was ± 15%. At higher concentrations precision was < 10%. Analyses were made under gold fluorescent lamps to avoid photodecomposition of the drug. The assay was specific for nifedipine and there was no on-column oxidation of the dihydropyridine nucleus. The nitrosopyridine derivative, formed upon exposure to light, or the carboxylic acid metabolites formed in-vivo, did not interfere with the assay.

Serum, nifedipine concentrations obtained after a single dose were expressed as mean ± s.e.m. as also were those obtained at steady state normalized to a 10 mg dose. The mean maximum serum concentration (C_{max}) and the mean time to achieve C_{max} (t_{max}) were obtained directly from the individual concentration-time data.

Further pharmacokinetic analysis was performed on the arithmetic mean serum concentration-time data rather than on the individual data sets for each patient as described by Cocchetto et al (1980). To calculate the mean terminal elimination rate constant of nifedipine (λz), we converted the observed serum concentrations after the single dose, or the dose-corrected serum concentrations at steady state, to their respective logarithms and calculated the arithmetic average of these log values for each sampling time. A cartesian plot of these values as a function of time was made and the mean terminal elimination rate constant was obtained by linear regression analysis of the terminal linear segment of this line.

The area under the curve (AUC) made by plotting the mean serum nifedipine concentration as a function of time from the single dose, or from the AUC from a plot of the mean dose-corrected serum concentration-time data from the steady state dose, was calculated from zero to 8 h using the linear trapezoidal rule. Cocchetto et al (1980) showed that the AUC so obtained was equal to the mean of individual values of AUC over the same time interval, as long as extrapolation was not used to estimate the AUC. The accumulation of nifedipine during multiple dosing was calculated according to Colburn (1983) as the ratio AUC (steady state)/AUC (test dose).

Results and discussion

Nifedipine was well tolerated. Four of five patients received 60 mg day^{-1}, the other patient was limited to 30 mg day^{-1} because of dizziness. There were no significant changes in blood pressure or heart rate in any of the patients after the single or multiple doses.

The mean serum concentrations after the first dose and those at steady state (after correcting for dose) are in Table 1. It may be seen from the large values of the standard error of the mean that there was wide variability in the absorption and disposition of the drug.

Table 1. Arithmetic mean (±s.e.m.) serum nifedipine concentrations (ng ml^{-1}) in 5 patients receiving single and multiple doses of nifedipine capsules.

Time (h)	Single dose, 10 mg	Steady state dose, 10 mg[a]
0·0	0	6·3 ± 1·8
0·5	24·5 ± 12·5	31·4 ± 19·4
1·0	25·5 ± 11·5	51·9 ± 20·8
2·0	18·4 ± 5·6	22·7 ± 10·1
3·0	12·0 ± 2·5	17·5 ± 4·9
4·0	10·3 ± 4·3	16·1 ± 5·0
5·0	10·4 ± 4·4	12·1 ± 3·5
6·0	9·3 ± 4·4	12·1 ± 3·6
7·0	8·1 ± 3·5	9·0 ± 4·5
8·0	8·1 ± 3·5	7·1 ± 2·5

[a] Dose-corrected concentrations.

This is consistent with the observations of others (Jakobsen et al 1979; Foster et al 1983; Kleinbloesem et al 1984a) and it is apparently related to large intersubject differences in first pass metabolism. After the single dose the mean C_{max}, as calculated from the arithmetic average of the individual C_{max} values was 33·3 ng ml^{-1}, while that of the corrected C_{max} at steady state was higher at 51·9 ng ml^{-1} but not significantly so (paired t, $P > 0{\cdot}05$). This latter result may reflect partial saturation of first pass nifedipine metabolism and a greater extent of bioavailability in comparison to a single dose. Idle & Sever (1983) postulated a saturable first pass effect to explain serum nifedipine concentration-dose relationships reported by Deanfield et al (1983) who used doses up to 120 mg day^{-1}. The daily doses we gave did not exceed 60 mg and resulted in mean single dose C_{max} values less than those reported elsewhere (Foster et al 1983; Raemsch & Sommer 1983) for a similar dosage form of nifedipine, while the mean steady state C_{max} values were similar to those of Deanfield et al (1983). The t_{max} values we obtained, 2·9 and 2·1 h, respectively, were not significantly different (paired t; $P > 0{\cdot}05$). Two of our subjects were slow absorbers as defined by a $t_{max} > 3{\cdot}5$ h and the remaining 3 subjects were fast absorbers with a $t_{max} < 2$ h. Foster et al (1983) found 3 of 12 subjects to be slow absorbers of nifedipine. Our mean t_{max} values after one dose were much larger than those of Foster et al (1983) and Raemsch & Sommer (1983) but the results from Foster et al at least, did not include values for slow absorbers.

Pharmacokinetic analysis of the individual serum nifedipine concentration-time data sets was not satisfactory as we were unable to define clearly a log linear

terminal decay phase in the concentration-time curves of some patients either after single or steady state dosing (see Table 1). This was most likely due to the slow absorption and multi-compartmental disposition kinetics of nifedipine (Kleinbloesem et al 1984a), the limited sampling times of the protocol, the assay sensitivity, and/or the non-linear disposition of the drug. However, we were able to obtain estimates of the mean values of λz and AUC by analysing mean serum concentration-time data. To avoid bias in estimating the mean value of λz from average concentration-time data, it was necessary to analyse the arithmetic mean of the *logarithmic* serum concentrations and not the arithmetic mean of the *actual* concentrations (Levy & Gibaldi 1975; Cocchetto et al 1980). We found that the mean λz after either a single dose or after a steady state dose was $0{\cdot}173\ h^{-1}$. The similarities we found in the mean λz after both regimens infers that the elimination kinetics of nifedipine were not altered by multiple dosing.

There are many ways of estimating the accumulation of a drug during multiple dosing. We chose to use the ratio of the areas under the serum nifedipine concentration-time curves from time 0 to 8 h for the steady state and single doses, respectively. This expression of accumulation has been recommended for drugs where the pharmacological effect is a function of the serum drug concentration (Colburn 1983). Kleinbloesem et al (1984a) showed that serum concentrations of nifedipine correlated directly with its effects on blood pressure and heart rate. Again, because of the difficulties in obtaining mean AUC values by analysing individual data sets we calculated the AUC values from the mean serum concentration-time curves (Cocchetto et al 1980), and these were 113·3 and 146·9 ng h ml^{-1} single and steady state doses. The values after a 10 mg dose were generally in agreement with those reported by Foster et al (1983) and Kleinbloesem et al (1984c). Recently, a bimodal frequency distribution of AUC values was reported to occur for nifedipine, suggesting the existence of two phenotypes: slow and fast metabolizers (Kleinbloesem et al 1984c). Fast metabolizers were the major phenotype and based on the individual AUC values in our study all 5 patients were fast metabolizers. The extent of accumulation calculated as 146·9/113·3 was 1·30 after multiple dosing. The accumulation of nifedipine after multiple dosing, although not reported previously, was not unexpected assuming its true elimination half-life was approximately 3 h or more. Theoretically the ratio $1/1 - e^{-\lambda zT}$ could be used to estimate the extent of its accumulation, assuming rapid absorption and distribution where T is the dosing interval (Colburn 1983). From this ratio, the extent of accumulation would be predicted to be approximately 1·2. Assuming a constant volume of distribution, the theoretical or actual accumulation of nifedipine after multiple doses based on AUC ratios may be solely determined by the value of λz and/or by a change in the extent of bioavailability. Since nifedipine is a high clearance drug whose elimination rate constant depends on hepatic blood flow, it would not be unusual to see an increase in the AUC at steady state due to changes in the extent of first pass metabolism concurrent with no apparent differences in half-life after single and multiple doses respectively (Kleinbloesem et al 1984c).

Thus we have provided evidence that serum nifedipine concentrations accumulated when the drug was dosed every 8 h to steady state. These findings may be useful in attempting to predict steady state serum concentrations and /or haemodynamic effects of nifedipine from single dose pharmacokinetic data.

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