Dose adjustment of nifedipine in hypertensive patients

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Summary. Ten patients with essential hypertension (WHO grade I–II) were treated in an open dose-adjustment study with the standard regimen of slow-release nifedipine 20 mg b.d. for 2 weeks and with an individualized dose for 6 weeks. The optimum dose, defined as that producing a pre-dose diastolic blood pressure (dBp) of 90 mmHg at steady state, was determined from the individual concentration-effect relationship after a test-dose of 20 mg.

On standard therapy, the reduction in pre-dose dBp was inadequate in 4 patients and it was excessive in 1 patient. After 2 weeks of individualized treatment, the required pre-dose antihypertensive effect was obtained in all patients. The individual doses required were 10 mg b.d., 10 mg t.d.s. 20 mg b.d., 20 mg t.d.s. and 20 mg q.d.s.

One patient dropped out of the study because of side effects. Loss of the antihypertensive effect was observed in one patient after 6 weeks of treatment.

On the optimized dose, the average value of the pre- and 2 h post-dose steady state nifedipine concentrations (27.6 µg/l) compared well with model-derived optimum concentrations (28.6 µg/l) (r = 0.9210).

The results show that the dose of nifedipine can be accurately predicted using the individual concentration-effect relationship after a single dose.

Key words: nifedipine, hypertension; concentration-effect relationship, individual dose, side effects

Slow-release formulations of nifedipine are widely used in the chronic treatment of hypertension [1–5]. Recent data indicate that the recommended dose of 20 mg nifedipine b.d. may be inadequate to achieve an optimum antihypertensive effect in some patients [6–8].

Previous investigations have shown that the maximum concentration of nifedipine (C_max) is proportional to the dose [9], and that the decrease in systolic and diastolic blood pressures is correlated with the plasma concentration-time profile. The concentration-effect curve is sigmoidal and can be described using a generalization of the equation for a hyperbola [8–11].

The aim of the present study was to predict, using the concentration-effect relationship in individual patients, the dose of slow-release nifedipine capable of maintaining a pre-dose diastolic blood pressure of 90 mmHg at steady state.

Subjects and methods

Ten patients, 7 men and 3 women, aged 40 to 62 y, and weighing 74 (9) kg, with mild to moderate essential hypertension (WHO Grade I–II) of 4–12 months duration, and an entry diastolic blood pressure of 107 (7) mmHg, took part in the study. All patients were non-smokers and none had taken antihypertensive medication in the 4 weeks preceding the study. Informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of the hospital.

The study design was open with a medication free run-in period of 1 week.

Single dose study

On Day 1, after an overnight fast each patient received 20 mg nifedipine orally, as a film-coated "biphasic" tablet, (Adalat® SL; Bayer AG, FRG) containing both conventional (fast-) and slow-release nifedipine. Standardized meals were taken 4 and 8 h after administration.

Blood samples 10 ml for determination of nifedipine concentrations were collected from an indwelling catheter in heparinized tubes before and 0.5, 1, 2, 3, 4, 6, 8 and 24 h after medication. To prevent photodegradation of nifedipine, the samples were taken under monochromatic yellow light. Nifedipine in plasma was determined by gas chromatography [12]. The coefficient of variation did not exceed 5% for within- and between-day determinations.

Blood pressure (mean of 2 readings) and the heart rates of the patients, after resting supine for 15 min, were measured immediately before blood collection using an automatic device (EBM 502/502D, FRG).

The decrease in supine diastolic blood pressure at rest produced by nifedipine (Δmm Hg) was fitted to the drug-plasma concentrations (C) by the sigmoidal E_max-equation [13]:

\[ E_{\text{max}} = \frac{C}{C_{\text{max}}} \]

\[ E_{\text{max}} = \frac{K_{\text{d}}}{K_{\text{d}} + C} \]

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Fig. 1. Plasma nifedipine concentration (Copt) required to achieve a target diastolic blood pressure of 90 mm Hg determined using individual concentration-effect relationships after a single dose of slow-release nifedipine 20 mg. E = decrease in diastolic blood pressure observed (o) and predicted (—) according to the Emax-equation, C = nifedipine plasma concentrations (Emax = maximum decrease, CES0 = concentration corresponding to 50% of Emax, and n = slope parameter)

\[ E = \frac{E_{\text{max}} \cdot C^n}{C_{\text{ES0}}^n + C^n} \]

where Emax = maximum decrease in blood pressure, CES0 = concentration corresponding to 50% of Emax, and n = slope parameter.

The model-derived concentration of nifedipine resulting in a diastolic blood pressure of 90 mm Hg was denoted as the optimum concentration (Copt; Fig. 1). The individualized optimum daily dose (Dind) of nifedipine was calculated as:

\[ D_{\text{ind}} \text{ (mg) } = C_{\text{opt}} \cdot \text{CL/f (l/h)} \cdot 24 \text{ h} \]

where CL/f is the apparent oral clearance of nifedipine, determined model-independently for each patient from the dose administered and the area under the concentration-time profile extrapolated to infinity (AUC; [14]). The dosing interval was determined from the duration of the antihypertensive effect in each patient.

Multiple dose study

In the following 2 weeks, each patient received a standard daily dose of 2 x 20 mg nifedipine. Thereafter, they were treated for 6 weeks with the individually determined optimum dose of nifedipine. Blood pressure, heart rate and plasma nifedipine concentrations were measured at 2-week intervals before and 2 h after the morning dose.

Non-linear least-squares regression analysis was used to estimate the effect-concentration relationship after the single dose of nifedipine. Pre- and post-treatment differences in blood pressure and heart rate were assessed using the Wilcoxon paired range test. Linear regression analysis was performed to test the correlation between the target effect and concentration and the observed values. Data are presented as mean (SD).

Results

Single dose study

After a test-dose of 20 mg slow-release nifedipine, the peak plasma concentration of 48.6 (19.6) µg/l occurred after about 1 (0.5) h, and 8 h later the concentration had fallen to 11 (6) µg/l.

The blood pressure was significantly lower than the pre-dose value between 0.5 and 8 h post-dose (P < 0.05). The maximal decreases in systolic and diastolic blood pressures amounted to 31 (8) and 23 (6) Δmm Hg, respectively (P < 0.05). The heart rate increased from 72 (9) to a maximum of 80 (9) min⁻¹ (P < 0.05).

The effect-time profile could be superimposed on the concentration-time profile in 3 patients. For those patients, the effect was fitted to the concentration using data for the entire observation period. In 7 patients, the peak