Haemodynamic Effects of Combined Oral Nifedipine and Sublingual Nitroglycerin in Patients with Chronic Stable Angina

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Summary. We examined the pharmacokinetics of nifedipine after acute and sustained oral therapy and the potential haemodynamic interaction between nifedipine and sublingual nitroglycerin in nine patients with chronic stable angina.

Nifedipine pharmacokinetics after a single oral dose and sustained dosing (three times daily for five days) were not significantly different. Single dose nifedipine produced a statistically significant decrease in standing and supine systolic and diastolic blood pressures when compared to placebo. A significant decrease in the supine systolic pressure was observed after sustained nifedipine therapy. Except for this change, other hypotensive effects of nifedipine after sustained therapy were not different to those of placebo, in spite of persistent plasma nifedipine concentrations after repeated dosing.

There were no observable correlations between nifedipine haemodynamics and pharmacokinetics in these patients, nor were there any significant haemodynamic interactions between sublingual nitroglycerin with either acute or sustained nifedipine treatment.

The transient haemodynamic effects of sublingual nitroglycerin were not potentiated by either acute or sustained nifedipine therapy.

Key words: nifedipine, nitroglycerin; nifedipine haemodynamics, nifedipine-nitroglycerin therapy, angina pectoris

Nifedipine is a 1,4-dihydropyridine calcium antagonist commonly used in the management of vasospastic and effort-induced angina pectoris, while sublingual nitroglycerin is a time-honored treatment for the acute relief of this disease. Both agents are frequently prescribed together in the management of angina pectoris. Since nifedipine and nitroglycerin are both potent vasodilators, it is important to determine whether these agents may be safely administered together. It is currently unknown whether the concomitant use of nifedipine and nitroglycerin results in a significant interaction at either the pharmacokinetic or the haemodynamic level, and whether these effects might depend on the duration of nifedipine therapy.

This study was designed, therefore, to ascertain the effects of sustained nifedipine therapy on its pharmacokinetics, and to determine if concomitant administration of nifedipine and sublingual nitroglycerin produces an additive haemodynamic response.

Methods and Materials

Nine patients (6 male and 3 female) with chronic stable angina receiving only nitroglycerin to treat chest pain were enrolled in this study. The patients ranged in age from 52 to 70 years (mean: 60.7 years).

The study was a randomized, double-blind, crossover trial involving two treatment phases with an intervening washout phase. Phase 1 consisted of nifedipine treatment, two 10 mg oral capsules given 3 times daily, for a period ranging from 4 to 9 days. Phase 2 consisted of nifedipine placebo dosing, with two capsules given 3 times daily, for a period of 4 to 6 days. A 2 to 4 day washout phase separated the two treatment phases. Patients were studied on the first and last day of each treatment phase. During each study day, patients were challenged with sublingual nitroglycerin (0.6 mg) before and at
5 Patients

NIFEDIPINE

WASHOUT

PLACEBO

4 Patients

PLACEBO

WASHOUT

NIFEDIPINE

MEAN DURATION OF TREATMENT (DAYS)

Fig. 1. Study protocol. The shaded area represents study assessment days during which a nitroglycerin sublingual tablet was administered at 0, 2 and 6 h after nifedipine dosing.

2 and 6 h after administration of the morning dose (Fig. 1).

Patients reported on the morning of each study day in the fasting state. Each patient was given his scheduled morning dose and monitored throughout the dosing interval. Blood samples were drawn before and at 0.5, 1, 2, 3, 4, 5, and 6 h after dosing for the analysis of nifedipine. At the same time, haemodynamic evaluation of standing and supine systolic and diastolic blood pressures were performed by sphygmomanometry. Before the morning dose and at 2 and 6 h after dosing, patients were challenged with a 0.6 mg nitroglycerin sublingual tablet. The assessment of the NTG challenge dose involved the determination of the haemodynamic response, followed by the collection of blood samples at 0, 2, 5, 10 and 15 min.

Plasma samples were handled to avoid the instability problems associated with nifedipine and nitroglycerin. Nifedipine plasma concentrations were determined by a sensitive and specific gas chromatographic assay with electron capture detection developed in our laboratories [1]. Nitroglycerin plasma concentrations were analyzed by a gas chromatographic method with electron capture detection [2]. It was established that neither drug interfered with the quantitation of the other.

The pharmacokinetic parameters for the nifedipine plasma data were calculated as follows: (a) The slope of the terminal disposition phase, \( \lambda_2 \), was estimated by fitting weighted \( 1/Y^2 \) post-peak concentration-time points to a monoexponential decay equation through the use of Nonlin [3] a non-linear regression computer analysis program. (b) The area-under-the-plasma-concentration-time curve (AUC) from time zero to infinity after single nifedipine dosing was estimated through the use of the Lagran computer program [4], with the extrapolated area from the last observed time point to infinity estimated by dividing the last observed concentration by the slope of the terminal phase. (c) The nifedipine steady-state AUC over the 8-h dosing interval was estimated through the use of Lagran, with the area from 6 to 8 h estimated by the log trapezoidal rule after computation of the expected nifedipine concentration at 8 h using the Nonlin parameters and assuming a monoexponential decay process. (d) The ratio of plasma clearance (CL) to bioavailability (f) for nifedipine was estimated by \( \text{CL}/\text{f} = \text{dose}/\text{AUC} \). Statistical analysis of the nifedipine pharmacokinetic data was accomplished by a two-tailed, paired Student t-test.

All haemodynamic data were subjected to a factorial analysis of variance (ANOVA). When the factor of interest was found to be statistically significant via the F distribution, Schelfie’s S-method was used to detect differences between the factor levels [5]. Haemodynamic effect versus time profiles were integrated by the trapezoidal rule over the 0–6 h interval to obtain the area-under-the-pharmacologic-effect versus time curve (AUPC). Average haemodynamic effects over the 0–6 h interval were computed by dividing the AUPC by 6 h. Correlations between the pharmacokinetic and haemodynamic data were assessed by the linear regression computer program Botherr in which error is assumed to be associated in both x and y parameters [6]. The Student’s t-distribution was used to assess the correlation for statistical significance. The level of significance for all statistical tests was alpha = 0.05.

Results

The nifedipine plasma concentration-time profiles after single and multiple dosing are shown in Fig. 2. Nifedipine pharmacokinetics were apparently unaltered after repeated dosing: the parameters of AUC,