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The effect of ketoconazole on the pharmacokinetics, pharmacodynamics and safety of nisoldipine

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Abstract *Objective*: The primary aim of the present study was to investigate the effect of ketoconazole on the pharmacokinetics of nisoldipine.
Methods: A single dose of nisoldipine 5 mg immediate-release tablet was administered either alone or in combination with ketoconazole 200 mg (4 days pre-treatment and concomitant administration) in a randomized crossover trial in seven healthy male Caucasian volunteers. Plasma concentration-versus-time profiles of nisoldipine and its metabolite M9 were determined.
Results: Pre-treatment with and concomitant administration of ketoconazole resulted in a 24-fold and 11-fold, increase in mean AUC and C_{max} of nisoldipine, respectively, compared with treatment with nisoldipine 5 mg alone. The ketoconazole-induced increase in plasma concentration of the metabolite M9 was of similar magnitude.
Conclusion: The interaction is attributed to inhibition of cytochrome 3A4-mediated first-pass metabolism. Ketoconazole and other antifungal drugs of the substituted imidazole type as well as other potent inhibitors of cytochrome 3A4 should not be used concomitantly with nisoldipine.

Key words Enzyme inhibition · Cytochrome P450 3A4 First-pass metabolism · Bioavailability

Introduction

Nisoldipine [(*R*, *S*)-3-isobutyl 5-methyl 1,4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylate], is a calcium antagonist of the 1,4-dihydropyridine class. It reduces vascular resistance and blood pressure by inhibiting calcium uptake of myocardial and smooth muscle cells. Nisoldipine has been approved in a number of countries in the immediate-release formulation (5 and 10 mg) as well as in the controlled-release dosage form (10, 20, 30 mg and 40 mg) for the treatment of hypertension and angina pectoris [1–4].

Nisoldipine is extensively metabolized by the cytochrome P450 (CYP) system, with the isoenzyme CYP 3A4 catalysing the dehydrogenation of the dihydropyridine ring [5–7]. Concomitant intake of drugs or food constituents that inhibit the CYP system – or more specifically its 3A4 isoenzyme – has been shown to result in increased systemic concentrations and sometimes pharmacodynamic effects of calcium antagonists [8]. The bioavailability of nisoldipine itself was increased by the inhibitors grapefruit juice [9] and cimetidine [10, 11]. Antifungal drugs of the substituted imidazole type are among the most potent inhibitors of CYP 3A4, and examples exist for clinically significant interactions, e.g. between ketoconazole and terfenadine [12] or tolbutamide [13], itraconazole and felodipine [14] or lovastatin [15], and fluconazole and nifedipine [16]. In light of these findings, the aim of the present study was to investigate the effect of ketoconazole on the pharmacokinetics of nisoldipine and its side-chain hydroxylated metabolite M9, the only metabolite with slight – although clinically not significant – pharmacological activity [10].

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Methods

Study design

The subjects were informed about the aims and risks of the study and gave their written informed consent to participate. The study was conducted in accordance with Good Clinical Practice guidelines and the 1975 declaration of Helsinki and its revisions after the protocol was approved by a local ethics committee (ethics committee at the North-Rhine Medical Council Düsseldorf, Germany). Before entering and after completion of the study, all volunteers underwent a thorough medical examination. None of the volunteers had any history of internal disease.

Either a single dose of 5 mg nisoldipine immediate-release tablet (Baymycard), or five subsequent once-daily doses of 200 mg

ketoconazole (Nizoral) in combination with 5 mg nisoldipine on day 5 were administered in a randomized non-blind crossover design with a 1-week washout. Plasma samples for assay of nisoldipine and metabolite M9 were collected on day 5 before administration and 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10 h and 24 h post administration (p.a.). Safety and tolerability were monitored by non-leading questioning and the determination of laboratory parameters, vital signs and electrocardiogram (ECG). Adverse events (AE) were categorized using COSTART [17] terms.

Eight healthy male Caucasian volunteers were enrolled. From day 1 through 4 the subjects were in the clinic only for administration of ketoconazole under medical supervision. On day 5 administration was at 0800 hours after an overnight fast and 24 h later the subjects left the clinic. Concomitant medications, caffeine and quinine- or grapefruit-containing preparations were not allowed during the study period.

Bioanalysis

Concentrations of nisoldipine and its 2-hydroxyisobutyl-metabolite M9 in plasma were determined using a validated gas-chromatographic assay with electron capture detection [18, 19]. The limit of quantification (LOQ) was 0.1 $\mu g \cdot l^{-1}$ (nisoldipine) and 1.0 $\mu g \cdot l^{-1}$ (M9). In quality control samples [with concentrations of 0.4, 2.0 and 8.0 $\mu g \cdot l^{-1}$ (nisoldipine) and 2.5, 5.0 and 8.0 $\mu g \cdot l^{-1}$ (M9)] analysed concurrently with study samples accuracy was 98–108% (nisoldipine)/100–107% (M9) and precision was 2.6–3.0% (nisoldipine)/2.3–3.8% (M9).

Pharmacokinetic and statistical evaluation

Pharmacokinetics were evaluated using non-compartmental techniques (Kincalc software for PC's, Bayer). Maximum plasma concentrations (C_{max}) and the times needed to reach these concentrations (t_{max}) were assessed by inspection of the concentration-versus-time plots. Area under the concentration-versus-time curve (AUC) was calculated using the log-linear trapezoidal rule up to the last time point with a concentration above LOQ (t_n) plus the extrapolated portion (AUC t_n–∞). Whenever a reasonable estimation of the terminal half-life was not possible, the AUC(0–t_n) was used instead. Apparent oral clearance (CL/f) was obtained by dividing dose by AUC. Non-categorical pharmacokinetic parameters are presented as geometric mean value and geometric standard deviation. The log-transformed data were subject to an analysis of variance and the resulting mean squared error was used to construct explorative 90% confidence intervals for the ratios of interest.

Results

Seven volunteers [aged 36 ± 8 years] were valid for safety, pharmacokinetic and pharmacodynamic evaluation (one subject dropped out due to an inter-current erysipelas before receiving the study drug).

Pharmacokinetics

The derived parameters of nisoldipine and metabolite M9 are given in Table 1. Figure 1 shows the individual and mean AUC(0–t_n) and C_{max} values of nisoldipine in both treatments.

Mean AUC(0–t_n) and C_{max} of nisoldipine were increased by 24- and 11-fold, respectively, while the same parameters for metabolite M9 were increased by 27- and

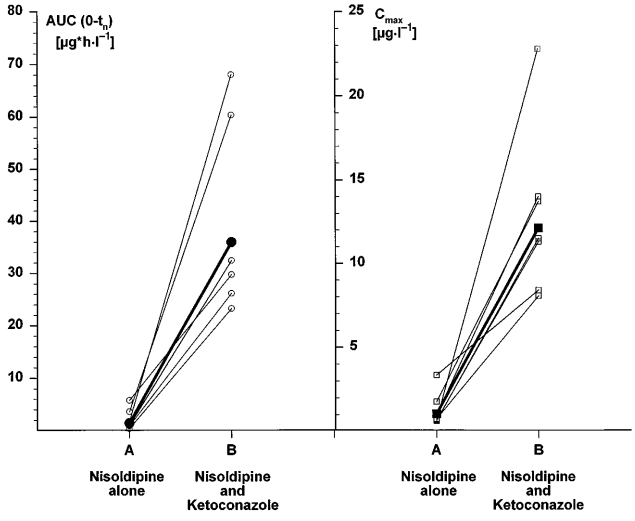

Fig. 1 Individual and geometric mean AUC (0–t_n) and C_{max} values of nisoldipine administered alone and in combination with ketoconazole

7-fold, respectively, with the nisoldipine + ketoconazole treatment compared with nisoldipine alone. Also, there was a trend towards increased t_{max} of nisoldipine in combination with ketoconazole. Following administration of 5 mg nisoldipine alone, concentrations in the elimination phase were often below the LOQ and did not allow an accurate estimation of the terminal half-life. There was a correlation between individual AUC(0–t_n) values following treatment with nisoldipine alone and the factor by which AUC was increased (coefficient of correlation: −0.84) i.e. the smaller the initial AUC of the drug, the higher the relative increase with concomitant ketoconazole. This resulted in a marked reduction in inter-subject variability in nisoldipine pharmacokinetics as indicated by geometric standard deviations in Table 1 (treatment B).

Safety and pharmacodynamics

In the nisoldipine + ketoconazole treatment one subject reported mild headache 6–8 h p.a. and a second subject experienced orthostatic dysfunction with moderate dizziness 4 h p.a. when getting into an upright position prior to lunch. He was laid down and observed until these complaints disappeared about 2.3 h later without further interventions. While systolic and diastolic blood pressure remained largely unaffected in the supine position, heart rate was already increased before the subject got upright. While standing, the subjective symptoms were accompanied by a drop in (mainly diastolic) blood pressure and a further increase in heart rate. Changes in ECG and clinical laboratory parameters were not clinically significant.

In comparison with nisoldipine alone, mean supine heart rate was increased from 1–2 h up to 10 h with a maximum increase of 16 beats $\cdot min^{-1}$ at 3 h after co-administration. Mean supine systolic blood pressure was

Table 1 Pharmacokinetic parameters of nisoldipine and its metabolite M9, presented as geometric mean and geometric standard deviation (*SD* in brackets); mean ratios with explorative 90% confidence intervals (*CI*) and min-max range; $n = 7$. *AUC* area under the concentration-versus-time curve, AUC (0–t_n) area under the concentration-versus-time curve from zero to the final time with a concentration above LOQ, C_{max} maximum plasma concentration, t_{max} time to reach C_{max}, $t_{1/2}$ elimination half-life, *CL/f* apparent oral clearance, *NC* not calculated

Parameter	A Nisoldipine alone geometric mean with (SD)	B Nisoldipine and ketoconazole geometric mean with (SD)	Ratio B:A Point estimate with (90% CI) and [min-max range]
Nisoldipine			
AUC [$\mu g \cdot h \cdot l^{-1}$]	NC	49.5 (1.78)	NC
AUC (0–t_n) [$\mu g \cdot h \cdot l^{-1}$]	1.42 (2.52)	35.9 (1.51)	24.4 (12.9–46.0) [5.2–61.7]
C_{max} [$\mu g \cdot l^{-1}$]	1.06 (1.85)	12.1 (1.42)	11.4 (5.8–22.4) [2.5–31.3]
t_{max} [h][d]	0.75 (0.5–2.0)	2.0 (0.75–4.0)	NC
$t_{1/2}$ [h]	NC	6.5 (1.28)[d]	NC
CL/f [$l \cdot h^{-1}$]	NC	101 (1.77)	NC
Metabolite M9			
AUC [$\mu g \cdot h \cdot l^{-1}$]	NC	117 (1.58)	NC
AUC (0–t_n) [$\mu g \cdot h \cdot l^{-1}$]	3.21 (1.33)[b]	79.2 (1.52)	27.1 (14.5–50.5) [10.8–43.7]
C_{max} [$\mu g \cdot l^{-1}$]	1.87 (1.44)[c]	12.8 (1.44)	6.7 (4.5–10.0) [3.5–10.9]
t_{max}[a] [h]	1.25 (0.5–2.0)	3.0 (1.5–5.0)	NC
$t_{1/2}$ [h]	NC	6.1 (1.34)	NC
CL/f [$l \cdot h^{-1}$]	NC	42.8 (1.58)	NC

[a] Calculated as median (min-max)
[b] $n = 5$; no measurable concentrations in other subjects
[c] $n = 6$; no measurable concentrations in other subject
[d] $n = 3$; fitting of terminal phase not possible in other subjects

decreased from 1 h up to 8 h, with the most obvious drug-related decrease 1 h after co-administration (−7.5 mmHg). Mean supine diastolic blood pressure was decreased from 1 h up to 6–8 h after co-administration (about −6 mmHg).

Discussion and conclusions

Nisoldipine, a drug with low oral bioavailability (3.9% [10], 8.4% [20]) due to pre-systemic metabolism, is liable to interact with potent inhibitors of CYP 3A4. Accordingly, a usual therapeutic dose of ketoconazole increased the AUC and C_{max} of nisoldipine more than 20-fold and ten-fold, respectively, in the present study. The magnitude of this interaction is comparable with the effect of itraconazole on lovastatin/lovastatin acid, another drug/metabolite with low oral bioavailability [15].

The interaction is likely to be caused by inhibition of first-pass metabolism, although an effect on systemic clearance cannot be ruled out, because the terminal elimination phase was not assessable after treatment with nisoldipine alone. The parallel increases in concentration of metabolite M9 and parent drug indicate that the side-chain hydroxylation of nisoldipine – in contrast to the oxidation of the dihydropyridine ring [7] – is not mediated by CYP 3A4.

Absolute effects of the co-administration of nisoldipine and ketoconazole on heart rate and blood pressure were rather small in normotensive volunteers. However, in view of the close relationship between nisoldipine plasma concentration and antihypertensive effect in the target population [21], this pharmacokinetic interaction would be expected to translate into a clinically significant pharmacodynamic interaction in patients at therapeutic nisoldipine doses. In addition to the absolute effects on heart rate and blood pressure, an increased risk of orthostatic dysfunction has to be considered. Therefore, nisoldipine should not be used in combination with ketoconazole. This also applies to its controlled-release formulation, although the magnitude of the interaction may be somewhat smaller, considering its absorption in the colon where first-pass metabolism is reduced [22]. Other antifungal imidazole drugs are likely to interact with nisoldipine in a similar fashion, as can be extrapolated from the effects of fluconazole on nifedipine (2.7-fold increase in AUC [16]) and itraconazole on felodipine (six-fold increase in AUC [14]). Both dihydropyridine drugs are also CYP 3A4 substrates. In view of their higher oral bioavailability compared with nisoldipine, the magnitude of the effect of either fluconazole or itraconazole on nisoldipine would therefore be expected to be significantly greater, i.e. comparable with that seen with ketoconazole. Ketoconazole, its congeners and other potent inhibitors of CYP3A4 should not be used concomitantly with nisoldipine.

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