Lack of effect of co-trimoxazole on the pharmacokinetics and pharmacodynamics of nifedipine

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The pharmacokinetics of nifedipine and its primary oxidised metabolite, M-I were studied in nine healthy volunteers following a single oral dose of 20 mg nifedipine alone or after pretreatment with oral co-trimoxazole. Following pretreatment with co-trimoxazole, no significant effect was detected on maximum plasma concentration, elimination half-life, or area under the plasma concentration-time curve of either nifedipine or M-I, nor on the blood pressure response to nifedipine.

Keywords co-trimoxazole drug interaction nifedipine pharmacokinetics

Introduction

In man, nifedipine is oxidised by hepatic microsomal cytochrome P450III_A isoenzymes (human PCN1 and PCN3) (Aoyama *et al.*, 1989; Gonzalez *et al.*, 1988). The potential exists, therefore, for interactions between nifedipine and other drugs metabolised by this same subfamily of mixed function oxidases. For example, nifedipine interacts with cimetidine (Smith *et al.*, 1987), cyclosporin (McFadden *et al.*, 1989) and quinidine (Oates *et al.*, 1988). An interaction between nifedipine and co-trimoxazole has not been documented but the latter decreases the clearance of phenytoin (Hansen *et al.*, 1975) and enhances the pharmacodynamic effects of warfarin (Hassall *et al.*, 1975; Tilstone *et al.*, 1977). We have seen a patient taking nifedipine who developed leg cramps and facial flushing when given co-trimoxazole, and whose symptoms resolved when the co-trimoxazole was withdrawn. These adverse effects may have been the consequence of elevated plasma nifedipine concentrations brought about by the concomitant administration of co-trimoxazole. The present study was designed to investigate the effects of co-trimoxazole on plasma concentrations of nifedipine and its primary oxidised metabolite, 2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester (M-I).

Methods

Protocol

The study received prior approval from the joint Health Authority/University Ethics Committee. Subjects were nine healthy, fully informed and consenting, non-smoking male volunteers aged 18 to 23 years, weighing 60 to 95 kg (mean 79 kg). All denied taking regular medication for 2 weeks prior to the study or drugs known to affect hepatic mixed function oxidases within the previous 2 months. Subjects were assigned, in random order, to two treatment periods in a cross-over, open study with a wash-out of 7 days between treatments.

The treatments consisted of a single oral dose of 20 mg nifedipine (2 × 10 mg Adalat capsules) either alone or following 3 days of pretreatment with oral co-trimoxazole 960 mg twice daily (Septtrin tablets). The co-trimoxazole was continued on the day of the nifedipine dose, making 4 days treatment in total.

On the day that nifedipine was taken, 10 ml blood samples were withdrawn from an intra-venous cannula which was kept patent with a solution of 4 u ml⁻¹ heparin. Samples were drawn prior to and then 30, 45, 60, 75, 90 min and 2, 3, 4, 6, 8 and 24 h after the nifedipine dose. Tubes were protected from light with

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aluminium foil. Blood was centrifuged in a dark-room and plasma stored at -20°C until analysis.

Drug analysis

Nifedipine and M-I were analysed in duplicate by capillary gas chromatography using a modification of the method of Schmid *et al.* (1988). Under sodium vapour illumination aqueous internal standard (nitrendipine $400\text{ }\mu\text{g l}^{-1}$, $100\text{ }\mu\text{l}$), tris buffer (20 mM , pH 9.0, $200\text{ }\mu\text{l}$) and toluene (1 ml) were added to plasma standard or unknown ($500\text{ }\mu\text{l}$), mixed (30 min) and centrifuged (2500 rev min^{-1} , 10 min). Toluene ($> 400\text{ }\mu\text{l}$) was aspirated and dispensed into amber glass autosampler vials (1.5 ml) and injected on-column ($0.2\text{ }\mu\text{l}$). Calibration curves were constructed from $0\text{--}180\text{ }\mu\text{g l}^{-1}$ for nifedipine and $0\text{--}80\text{ }\mu\text{g l}^{-1}$ for M-I and were linear ($r > 0.995$). Limits of detection were $1.0\text{ }\mu\text{g l}^{-1}$, nifedipine, and $0.5\text{ }\mu\text{g l}^{-1}$, M-I, respectively. The intra-assay coefficients of variation were between 3.6% and 6.4% for nifedipine and between 4.2% and 22% for M-I, whereas the inter-assay coefficients of variation were between 2.2% and 10.8% for nifedipine and between 3.8% and 8.5% for M-I. Random repeats of samples (10%) were well correlated ($r = 0.992$) and the intra-assay coefficients of variation of the quality controls used ($72\text{ }\mu\text{g l}^{-1}$, nifedipine and $30\text{ }\mu\text{g l}^{-1}$, M-I) were no greater than 15%.

Clinical measurements

Supine systolic and diastolic blood pressures (Korotkoff, Phase V) were recorded in duplicate by one observer using a random zero sphygmomanometer at 0, 30, 60, 90 min and then 2, 3, 4, 6 and 8 h after nifedipine administration.

Pharmacokinetic and statistical analysis

The data were fitted by a two compartment model using a non-linear extended least squares regression programme (KINET, Dr N. S. Oates, Department of Pharmacology and Toxicology, St Mary's Hospital Medical School, London). Maximum plasma concentration (C_{max}) was estimated as the highest value on the plasma drug concentration profile and the time to reach this concentration was designated t_{max} . The elimination rate constant λ_z was obtained by least squares regression of the log linear portion of the plasma concentration vs time plot. The elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/\lambda_z$. The area under the plasma drug concentration vs time curve (AUC) was determined using the trapezoidal rule and extrapolated to infinity.

The amount extrapolated was less than 3.2% of the total AUC.

Statistical analysis was performed using Student's *t*-test for paired data (pharmacokinetic data). Systolic and diastolic blood pressure were analysed on a point by point basis by analysis of variance with repeated measures. A value of $P \leq 0.05$ was taken to be statistically significant.

Results

Mean log plasma concentration time profiles for nifedipine and M-I with and without pretreatment with co-trimoxazole are shown in Figure 1. When compared with the control period, values for AUC, C_{max} , and $t_{1/2}$ were unchanged after pretreatment with co-trimoxazole (Table 1). Mean nifedipine/M-I ratios measured at C_{max} were not significantly changed before (2.3 ± 0.6) and after (2.1 ± 0.5) pretreatment with co-trimoxazole. The study design was sufficiently sensitive to detect a 29 to 33% change in AUC, with an α value of 0.05 and a β value of 0.1 and

Figure 1 Plasma concentrations of a) nifedipine and b) M-I in the presence (●: dotted lines) and absence (○: solid lines) of co-trimoxazole. Symbols represent mean plasma concentrations ($\pm$ s.e. mean) after oral administration of nifedipine (20 mg).

Table 1 Pharmacokinetic parameters for nifedipine and M-I in the presence and absence of co-trimoxazole. Values shown mean $\pm$ s.d. ($n = 9$)

	C_{max} (ng ml ⁻¹)	Nifedipine AUC (ng ml ⁻¹ h)	$t_{1/2}$ (h)
Co-trimoxazole pretreatment	137.1 $\pm$ 39.2	366 $\pm$ 105	2.5 $\pm$ 1.1
Control	172.6 $\pm$ 51.2	324 $\pm$ 92	2.1 $\pm$ 0.5
Data pair differences	35.3 $\pm$ 66.9	42.2 $\pm$ 86.2	0.42 $\pm$ 1.17
		M-I	
Co-trimoxazole pretreatment	66.2 $\pm$ 23.7	165 $\pm$ 33	3.5 $\pm$ 1.5
Control	78.9 $\pm$ 26.4	179 $\pm$ 40	3.1 $\pm$ 1.7
Data pair differences	12.7 $\pm$ 28.9	14.2 $\pm$ 42.7	0.38 $\pm$ 2.27

a 67 to 88% change in $t_{1/2}$. The t_{max} values for nifedipine and M-I were coincidental with the time of the first blood sample, i.e. 30 min, in all but one volunteer (t_{max} 45 min).

Supine systolic and diastolic blood pressures were not significantly lowered after the nifedipine dose following pretreatment with co-trimoxazole.

Discussion

There are only a few reported interactions between co-trimoxazole and other drugs and some of these may be ascribed to effects on renal excretion (Ringden *et al.*, 1984; Thompson *et al.*,

1983) or to a pharmacodynamic interaction (O'Reilly & Motley, 1979) rather than effects on hepatic metabolism. It may therefore be coincidence that the drugs with which it has been reported to interact are metabolised by cytochrome P450 enzymes. The lack of effect on nifedipine disposition in the present study suggests that at therapeutic concentrations, neither sulphamethoxazole nor trimethoprim (the constituents of co-trimoxazole) inhibits nifedipine metabolism.

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References

- Aoyama, T., Yamano, S., Waxman, D. J., Lapenson, D. P., Meyer, U. A., Fischer, V., Tyndale, R., Inaba, T., Kalow, W., Gelboin, H. V. & Gonzalez, F. J. (1989). Cytochrome P-450 hPCN3, a novel cytochrome P-450 IIIA gene product that is differentially expressed in adult human liver. *J. biol. Chem.*, **264**, 10388–10395.
- Gonzalez, F. J., Schmid, B. J., Umeno, M., McBride, O. W., Hardwick, J. P., Meyer, U. A., Gelboin, H. V. & Idle, J. R. (1988). Human P450PCN1: Sequence, chromosome localization, and direct evidence through cDNA expression that P450PCN1 is nifedipine oxidase. *DNA*, **7**, 79–86.
- Hansen, J. M., Siersback-Nielsen, K., Skovsted, L., Kampmann, J. P. & Lumholtz, B. (1975). Potentiation of warfarin by co-trimoxazole. *Br. med. J.*, **2**, 684.
- Hassall, C., Feetam, C. L., Leach, R. H. & Meynell, M. J. (1975). Potentiation of warfarin by cotrimoxazole. *Lancet*, **ii**, 1155.
- McFadden, J. P., Pontin, J. E., Powles, A. V., Fry, L. & Idle, J. R. (1989). Cyclosporin decreases nifedipine metabolism. *Br. med. J.*, **299**, 1224.
- Oates, N. S., Feher, M. D., Perry, H. E., Schmid, B. J., Sever, P. S. & Idle, J. R. (1988). Influence of quinidine on nifedipine plasma pharmacokinetics. *Br. J. clin. Pharmacol.*, **25**, 675P.
- O'Reilly, R. A. & Motley, C. H. (1979). Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. *Ann. int. Med.*, **91**, 34.
- Ringden, O., Myrenfors, P., Klintmalm, G., Tyden, G. & Ost, L. (1984). Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. *Lancet*, **i**, 1016–1017.
- Schmid, B. J., Perry, H. E. & Idle, J. R. (1988). Determination of nifedipine and its three principal metabolites in plasma and urine by automated electron-capture capillary gas chromatography. *J. Chromatogr.*, **425**, 107–119.
- Smith, S. R., Kendall, M. J., Lobo, J., Beerah, A., Jack, D. B. & Wilkins, M. R. (1985). Ranitidine and cimetidine; drug interactions with single dose and steady-state nifedipine administration. *Br. J. clin. Pharmacol.*, **23**, 311–315.
- Thompson, J. F., Chalmers, D. H. K., Hunnisett, A. G. W., Wood, R. F. M. & Morris, P. J. (1983). Nephrotoxicity of trimethoprim and cotrimoxazole in renal allograft recipients treated with cyclosporine. *Transplantation*, **36**, 204–206.
- Tilstone, W. J., Gray, J. M. B., Nimmo-Smith, R. H. & Lawson, D. H. (1977). Interaction between warfarin and sulphamethoxazole. *Postgrad. med. J.*, **53**, 388.

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