The interaction between i.v. theophylline and chronic oral dosing with slow release nifedipine in volunteers

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1 Eight healthy volunteers received a 5 min i.v. infusion of lysine theophylline, equivalent to 197 mg anhydrous theophylline, both before (day 1) and during (day 5) steady state chronic oral dosing with slow release nifedipine 20 mg 12 hourly.

2 A theophylline pharmacokinetic profile was performed on day 1 and day 5 and a nifedipine pharmacokinetic profile was performed on day 4 and day 5.

3 The greatest difference in serum theophylline concentrations was seen at the first sampling time (5 min after completion of the infusion) with a mean concentration of 9.9 mg l⁻¹ during nifedipine administration and 14.6 mg l⁻¹ with theophylline alone. Thereafter, the difference fell to approximately 1 mg l⁻¹ until 6 h when they became almost identical.

4 Repeated measures analysis of variance using the theophylline serum concentrations at each of ten time points over 8 h as the repeated measures showed a small but significant effect of nifedipine ($F_{(1,151)} = 7.0$, $P < 0.01$) on serum theophylline concentrations.

5 Mean volume of distribution (V) rose from 0.33 ± 0.07 to 0.39 ± 0.06 l kg⁻¹ corrected body weight (CBW) in the presence of nifedipine ($t = 2.23$, $P = 0.052$). Theophylline clearance, area under the curve to 8 h AUC (0–8), area under the curve to infinity AUC (0– ∞) and elimination half-life ($t_{1/2}$) did not change appreciably.

6 No statistically significant changes in nifedipine pharmacokinetics occurred in the presence of theophylline.

Keywords theophylline slow release nifedipine pharmacokinetic interaction

Introduction

Calcium antagonists are being used increasingly for both hypertension and angina. Although clinically important pharmacokinetic drug interactions have been described with verapamil (Klein *et al.*, 1980), the situation with regard to nifedipine is unclear. A small but significant rise in trough plasma digoxin concentrations occurred during chronic oral digoxin dosing when nifedipine was coadministered to 12 volunteers (Belz *et al.*, 1981). No significant changes in digoxin plasma clearance or V were seen in eight volunteers (Pedersen *et al.*, 1982). Similar findings

were reported by Zylberkatz *et al.*, (1984). No interaction studies have reported measurements of nifedipine concentrations.

When asthma coexists with hypertension or angina, β -adrenoceptor antagonists are contraindicated but calcium antagonists can be given safely. Now that twice daily preparations are available, this group of drugs is likely to become more widely used for hypertension. Theophylline preparations are frequently used in the treatment of asthma but require adequate serum concentrations of theophylline to optimise

therapy. We therefore decided to investigate a possible pharmacokinetic interaction between theophylline and nifedipine.

We chose to study the effect of oral slow release nifedipine on i.v. rather than oral theophylline disposition as this would enable us to study V and clearance more accurately. In addition, this route of administration is usual in acute severe asthma.

Methods

Eight healthy volunteers (four male) aged 21–34 years and weighing 52–86 kg received an i.v. infusion of lysine theophylline containing 197 mg anhydrous theophylline on day 1 of the study. Blood was taken at 10, 20, 40 min, 1, 1.5, 2, 3, 4, 6 and 8 h for determination of serum theophylline concentration. At 21.00 h on day 1, volunteers started taking slow release nifedipine at a dose of 20 mg and repeated this 12 hourly for a total of 8 doses (up to and including 09.00 h on day 5). On day 4, starting at 09.00 h, blood samples were taken at identical times to day 1 and additionally at 12 h for determination of serum nifedipine concentrations. At 09.00 h on day 5 an identical infusion of lysine theophylline was given and blood samples were taken as previously for determination of both theophylline and nifedipine serum concentrations.

Serum theophylline concentrations were determined using an enzyme mediated immunoassay technique (EMIT) (Chang *et al.*, 1982). Both the within assay and between assay coefficient of variation (CV) at 5.4 mg l⁻¹ were < 4%. The presence of nifedipine in serum at 100 µg l⁻¹ did not alter the measurement of theophylline. Serum nifedipine concentrations were determined using a specific high performance liquid chromatographic method that was capable of resolving B4759, the nitropyridine analogue of nifedipine—a metabolite. The CV at 10 µg l⁻¹ was < 5%. The limit of detection was 2 µg l⁻¹ (Debbas *et al.*, 1986).

All blood and serum samples for nifedipine assay were handled in sodium light or in foil wrapped containers when exposed to daylight or tungsten light. From these concentration–time profiles, clearance, apparent $t_{1/2}$ and AUC (0–12), were calculated for nifedipine using STRIPE (Johnston & Woollard, 1983). In order to reduce further the sum of squares for the pharmacokinetic model, nifedipine concentration–time profiles were further analysed using a non linear regression program (SIMP) (Johnston, 1985) to optimise the parameters in the equation that had been derived using STRIPE. Clearance,

$t_{1/2}$, V , AUC (0–8) and AUC (0–∞) were also calculated for theophylline using STRIPE. Pharmacokinetic variables were derived for each pair of days and compared using Student's paired t -test.

Only AUC (0–12) and apparent $t_{1/2}$ for nifedipine will be presented as clearance is derived directly from dose and AUC (0–12). Further, the calculation of clearance requires knowledge of the bioavailability which was not available for all eight volunteers. However, because the conversion of AUC to clearance involves a reciprocal transformation, statistical significance testing will produce different results for clearance versus AUC. For this reason the results of the paired t -test performed on the clearance data will be presented assuming that the fraction absorbed was consistent on the two nifedipine profile days. Both clearance and V for theophylline were expressed per kg CBW to reduce interindividual variation due to differences in adiposity (Melethil *et al.*, 1982). CBW was defined as either total body weight or ideal body weight (Gal *et al.*, 1978) whichever was the lesser.

Two-way repeated measures analysis of variance (ANOVA) was performed on the individual serum concentrations for the whole of the sampling period on each day to identify simultaneously variance due to subjects and treatments.

Results

Theophylline

The comparisons of derived pharmacokinetic variables between day 1 and day 5 showed no statistically significant differences (Figure 1). However, values were not identical and differences of biological importance were seen for V . On average V rose by 16.8% from 0.33 to 0.39 l kg⁻¹ CBW during nifedipine dosing ($t = 2.23$, $P = 0.052$). The mean rise in uncorrected V was 3.7 l. The mean serum theophylline concentrations were consistently lower in the presence of nifedipine than without it for 6 h after dosing. ANOVA demonstrated a small but statistically significant fall in the serum concentrations of theophylline in the presence of nifedipine ($F_{1, 151} = 7.0$, $P < 0.01$). The greatest difference was at 10 min with mean serum concentrations of 14.6 mg l⁻¹ without nifedipine and 9.9 mg l⁻¹ with nifedipine (Figure 2).

Nifedipine

Mean serum concentrations of nifedipine peaked 90 min after dosing in the absence of theophylline

Figure 1 Individual (—) and mean (---) value for theophylline clearance ($\text{ml min}^{-1} \text{kg}^{-1}$ corrected body weight (CBW)), volume of distribution (V) (l kg^{-1} CBW), AUC (0–8) ($\text{mg l}^{-1} \text{h}$), AUC (0– ∞) ($\text{mg l}^{-1} \text{h}$) and $t_{1/2}$ (h), for eight volunteers prior to (T) and during (T + N) chronic dosing with slow release nifedipine 20 mg 12 hourly.

Figure 2 Serum theophylline concentration–time profiles for eight volunteers after 197 mg of theophylline i.v. prior to (●—) and during (○—) chronic dosing with slow release nifedipine 20 mg 12 hourly.

(day 4) and at 2 h when theophylline was present (day 5). There were no statistically significant differences in mean t_{max} on the two days: 1.67 h on day 4 and 2.2 h on day 5 ($t = 1.7$, $P < 0.1$). Both trough and peak concentrations were almost identical on the two days. ANOVA showed no effect of theophylline on serum nifedipine concentrations over the whole time period. The derived pharmacokinetic variables clearance, AUC (0–12) and apparent $t_{1/2}$ showed no statistically significant differences between the two days (Figure 3). Serum concentrations at 0 h did not differ significantly from concentrations at 12 h (10.6 and $13.5 \mu\text{g l}^{-1}$, respectively on day 4 ($t = 0.83$, $P < 0.4$), 8.6 and $10.8 \mu\text{g l}^{-1}$, respectively on day 5 ($t = 1.6$, $P > 0.1$)).

Discussion

The lack of effect of theophylline on slow release nifedipine pharmacokinetics during chronic dosing is an important new observation. An important question not answered by this study is whether absolute nifedipine bioavailability is affected by theophylline. Indirect evidence exists to suggest that this might be so for erythromycin bioavailability (Iliopoulou *et al.*, 1982; Hildebrandt *et al.*, 1983).

Apparent $t_{1/2}$ is calculated from λ_z and reflects the decay in serum concentrations over the dosing interval whilst absorption is taking place. It is

Figure 3 Individual (—) and mean (---) values for nifedipine AUC (0–12) ($\mu\text{g l}^{-1} \text{h}$) and apparent $t_{1/2}$ (h) for eight volunteers in the absence (N) and presence (N + T) of theophylline.

thus a measure of the delayed release of nifedipine as well as the true $t_{1/2}$ of the drug and is a clinically relevant parameter when assessed over an appropriate dosing interval.

The difference in serum concentrations of theophylline on days 1 and 5 during the early part of the sampling period suggests that the volume of distribution of theophylline was greater in the presence of nifedipine. The mean increase in V was $0.06 \text{ l kg}^{-1} \text{ CBW}$ (3.8 l) and although this did not quite reach statistical significance ($P = 0.052$), it is probably a genuine effect in view of the statistically significant change in serum concentrations. The marked difference in the serum theophylline concentrations at the first sampling time may have been

due to an increased rate of distribution but this could not account for the consistently lower concentrations throughout the next 6 h. A change in V could be caused by a change in protein binding of theophylline although we do not have data to support this hypothesis. A decrease in bound theophylline caused by nifedipine could cause lower serum theophylline concentrations and therefore an increase in V .

We are grateful to Bayer UK Ltd for financial assistance and the serum nifedipine assays, Laboratories for Applied Biology, London for supplies of lysine theophylline and to Louise Phelps for secretarial help. AJ is supported by the Synthelabo Foundation.

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(Received 3 January 1985,
accepted 24 November 1985)