PHARMACOKINETIC INTERACTION BETWEEN THEOPHYLLINE AND ERYTHROMYCIN

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- 1 The pharmacokinetics of a single intravenous dose of theophylline alone and during the fifth day of treatment with 500 mg erythromycin every 8 h was studied in six healthy subjects.
- 2 At the same time the pharmacokinetics of erythromycin at steady-state on the fourth day of the treatment (alone) and the fifth day (during the theophylline co-administration) were also studied.
- 3 Mean $\pm$ s.d. theophylline clearance was decreased from 62 ± 15.4 to 53 ± 10.3 ml min⁻¹ ($P < 0.05$) and elimination half-life rose from 7.1 ± 1.9 to 7.7 ± 2 h ($P < 0.05$) when erythromycin was co-administered.
- 4 Mean $\pm$ s.d. erythromycin area under the curves (0–8 h) and (0– ∞) were reduced from 6.09 ± 3.2 to 3.8 ± 2.5 μ g ml⁻¹ h and 7.2 ± 3.6 to 5.0 ± 2.9 μ g ml⁻¹ h ($P < 0.05$) in the presence of theophylline. Mean steady state and maximum steady state concentrations were also reduced from 0.75 ± 0.4 to 0.47 ± 0.3 μ g ml⁻¹ ($P < 0.05$) and 1.45 ± 0.87 to 0.85 ± 0.51 μ g ml⁻¹ ($P < 0.05$) respectively.
- 5 The potential clinical implications of this indication should be considered.

Introduction

Controversy exists about the pharmacokinetic interaction of theophylline and macrolide antibiotics. Early studies by Weinberger *et al.* (1977) showed that troleandomycin reduced the metabolic clearance and prolonged the elimination half-life of theophylline, but Pfeifer *et al.* (1979) found no overall change in kinetics of i.v. aminophylline after short exposure to erythromycin. Recent studies in normal volunteers have shown a fall in clearance and rise in elimination half life of oral theophylline after long exposure to erythromycin (Renton *et al.*, 1981; May *et al.*, 1982). Branigan *et al.* (1981) reported the same pattern of results in asthmatic patients accompanied by an increase in apparent volume of distribution but no change in apparent clearance.

Although the phenomenon has been extensively studied all reports focus on theophylline which is the drug whose kinetics may be said to benefit from the presence of the antibiotic, while the possible effect of the bronchodilator on erythromycin kinetics has been ignored. In this study therefore we have examined the pharmacokinetics of both drugs, alone and in combination, to investigate whether a mutual interaction exists. This is an important consideration in view of the increasing use of erythromycin as a first choice antibiotic especially against severe respiratory infections (e.g. Legionnaire's disease, *Mycoplasma pneumoniae*).

Methods

Six healthy subjects, four female and two male aged 20 to 32 years (weight 52 to 75 kg) were selected on the basis of medical history and physical examination (free from hepatic, respiratory, cardiac disease or allergic reaction to erythromycin). One of the men was a mild smoker. All subjects gave written informed consent. They refrained from other drug treatment throughout the study period (2 weeks) and were requested to abstain from alcohol, dietary methylxanthines and excessive nicotine 24 h before each theophylline injection and during the sampling period.

The study was a cross-over type with each subject serving as his own control. Each subject received a single intravenous infusion of 250 mg theophylline (Lysine-theophylline, Laboratories for Applied Biology, U.K.), in 50 ml saline over 5 min using a constant infusion pump. Venous blood samples were drawn into plain tubes immediately before, at the end, 10, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after the end of the infusion from an indwelling cannula. After centrifugation serum was frozen at -20°C until analysed (theophylline alone). Each subject after 1 week's interval commenced a 5 day course of 500 mg erythromycin stearate (Erythrocin, Abbott Laboratories, U.K.) orally every 8 h. In the morning of the fourth day blood samples were drawn immediately before and for 8 h

after the morning dosing as above for analysis (erythromycin alone). On the fifth day of the antibiotic treatment the same (250 mg) dose of theophylline was infused into each subject and blood samples were collected for 24 h as before for theophylline and (up to 8 h only) for erythromycin analysis. The last three erythromycin doses were taken regularly at 8 h intervals during the sampling period starting immediately before the infusion of theophylline.

Theophylline serum concentrations were estimated by EMIT and erythromycin by microbiological assay, using *Sarcina lutea* NCTC 8340 as test organism (the within assay and between assay coefficients of variation were less than 12%) (Iliopoulou *et al.*, 1981). It was established that neither of the drugs interfered with the assay of the other.

Samples obtained during the administration of erythromycin alone and in combination with theophylline were also analysed for erythromycin protein binding by equilibrium dialysis against isotonic phosphate buffered saline pH 7.3 (Dulbecco 'A' Oxoid Limited, U.K.) across a 11.5 μ m cuprophane membrane in 1 ml acrylic cell. The cells were rotated 45 times min^{-1} at 37°C for 6 h. Erythromycin concentrations were measured on both sides of the membrane by the above assay. It was established that equilibrium was reached within 6 h. The coefficients of variation for percentage within and between assays were less than 3% and 13% respectively.

Pharmacokinetic parameters were calculated for theophylline assuming an open two compartment intravascular and for erythromycin an open one compartment extravascular model. Rate constants and half-lives were derived from the log concentration time curves by least squares regression and the method of residuals, and area under the curve ($\text{AUC}_{0-24\text{h}}$ or $\text{AUC}_{\tau-\tau+1}$) by the trapezoidal rule for both drugs.

The areas under the curve $\text{AUC}_{0-\infty}$ for theophylline and $\text{AUC}_{\tau-\infty}$ for erythromycin were calculated using equations:

$$\text{AUC}_{0-\infty} = \text{AUC}_{0-24\text{h}} + \text{AUC}_{24\text{h}-\infty}$$

and

$$\text{AUC}_{\tau-\infty} = \text{AUC}_{\tau-\tau+1} + \text{AUC}_{\tau+1-\infty}$$

$$\text{AUC}_{24\text{h}-\infty} = \frac{Cx}{\beta}$$

$$\text{AUC}_{\tau+1-\infty} = \frac{Cx}{\text{Kel}}$$

where Cx = last blood concentration; β = elimination rate constant; Kel = elimination rate constant; τ = dosing interval.

For theophylline volume of distribution (V_d) and clearance (CL) the following formulae were used:

$$V_d = \frac{D}{\text{AUC}_{0-\infty} \cdot \beta} \text{ and } \text{CL} = \frac{D}{(A/\alpha + B/\beta)}$$

where D = dose, β = elimination rate constant. α = distribution rate constant and B and A are the corresponding intercepts of these exponents.

Erythromycin steady state concentration (C) was derived from the formula:

$$C = \frac{\text{AUC}_{\tau-\tau+1}}{\tau}$$

where τ = dosing interval.

The two-tailed paired sample Student's *t*-test was used to test the significance of difference between the two treatment periods for each individual drug.

Results

The mean ($\pm$ s.e. mean) serum theophylline concentrations of the six subjects before and during erythromycin treatment are shown in Figure 1. The mean ($\pm$ s.d.) theophylline elimination half-life increased from 7.1 ± 1.9 to 7.7 ± 2.0 h ($t = 3.3$, $P < 0.05$) and the mean clearance fell from 62 ± 15.4 to 53 ± 10.3 ml min^{-1} ($t = 3.3$, $P < 0.05$) in the presence of erythromycin. There was little change in either mean distribution half-life (0.27 ± 0.26 to 0.35 ± 0.32 h) or distribution volume (36 ± 3.7 to 34 ± 4.2 l), ($t = 0.57$, $P > 0.5$ and $t = 1.02$, $P > 0.05$ respectively). $\text{AUC}_{0-24\text{h}}$ and $\text{AUC}_{0-\infty}$ tended to increase from 63.1 ± 15.4 to 69 ± 14.9 and 72 ± 21 and 81 ± 20 $\mu\text{g ml}^{-1}$ h respectively, but the changes were not statistically significant ($t = 1.27$, $P > 0.05$ and $t = 1.82$, $P > 0.05$). The results for each individual are presented graphically in Figure 2.

The mean ($\pm$ s.e. mean) serum erythromycin levels measured in the six subjects before (day 4 of treatment) and during (day 5) intravenous theophylline are displayed in Figure 3. During theophylline there were large falls in the area under the erythromycin concentration-time curves, mean ($\pm$ s.d.) $\text{AUC}_{0-8\text{h}}$ fell from 6.1 ± 3.2 to 3.8 ± 2.5 $\mu\text{g ml}^{-1}$ h ($t = 3.94$, $P < 0.05$) and mean $\text{AUC}_{0-\infty}$ fell from 7.2 ± 3.6 to 5.0 ± 2.9 $\mu\text{g ml}^{-1}$ h ($t = 3.59$, $P < 0.05$). At the same time the subjects mean erythromycin elimination half-life was increased from 2.8 ± 0.6 to 3.5 ± 0.67 h but this change was not significant ($t = 1.84$, $P > 0.05$). No significant alteration in the mean absorption half-life (0.65 ± 0.34 to 0.77 ± 0.6 h) was also observed ($t = 0.53$, $P > 0.5$). The results for each individual are illustrated in Figure 4.

The mean steady state concentration (C) was reduced significantly from 0.75 ± 0.40 to 0.47 ± 0.3

Figure 1 Theophylline (single dose) serum concentrations plotted against time as mean $\pm$ s.e. mean from six subjects before (O) and during erythromycin co-administration (●).

Figure 2 Graphical representation of the mean (---) and the individual subject (—) values and paired *t*-test significance of various pharmacokinetic variables derived from administration of theophylline alone (T) and in combination with erythromycin (T + E). * indicates values from the only smoker of the study.

Figure 3 Erythromycin (multiple dose) serum concentrations (within a dosing interval at the plateau) plotted against time as a mean $\pm$ s.e. mean from six subjects before (fourth day, —) and during theophylline co-administration (fifth day, ---). See text for description of treatment schedules.

Figure 4 Graphical representation of the mean (-----) and individual subjects (————) values and paired *t*-test significance of various pharmacokinetic parameters derived from erythromycin treatment alone (E) and in combination with theophylline (E + T), See text for description of treatment schedules.

$\mu\text{g ml}^{-1}$ ($t = 3.96$, $P < 0.05$). The observed maximum steady state serum concentration ($C_{\text{max}}^{\text{ss}}$) was also reduced from 1.45 ± 0.87 to $0.85 \pm 0.51 \mu\text{g ml}^{-1}$ ($t = 3.07$, $P < 0.05$) but the change in minimum steady state concentration ($C_{\text{min}}^{\text{ss}}$) did not reach significance. The actual time to reach maximum concentration ($t_{\text{max}}^{\text{ss}}$) tended to be prolonged from 100 ± 30 to 117.5 ± 46.8 min but not significantly. Finally, although the change did not reach statistical significance, erythromycin percentage protein binding tended to decrease from 72 ± 4 to $68 \pm 6\%$ ($t = 2.19$, $P > 0.05$), in the presence of theophylline, and therefore the unbound to total serum concentration ratio was 0.28 and 0.32 respectively.

Discussion

In the present study 5-day treatment with erythromycin impaired the clearance, prolonged the elimination half-life and tended to increase the area under the curve without altering the volume of distribution of single intravenous doses of theophylline in six healthy subjects. These findings support previous work of Prince *et al.* (1980), Renton *et al.* (1981) and May *et al.* (1982) in normal subjects and Branigan *et al.* (1981) in asthmatic patients (although the area under the curve and clearance were not altered in the latter study). Our results as well as those mentioned above reflect the changes in at least one of the 'primary' pharmacokinetic parameters such as clearance or volume of distribution (in the case of intravenous administration). In fact, elimination half-life is a 'secondary' parameter that changes as a function of both clearance and volume of distribution (approximate relationship $t_{1/2} \approx 0.7 V_d \text{CL}$ (Benet & Sheiner, 1980)). Thus, in our case elimination half-life

was increased because the total clearance of the theophylline was decreased. Theophylline is eliminated primarily by biotransformation in the liver mixed function oxidase system (Lohmann & Miech, 1976; Ogilvie, 1978; Pfeifer *et al.*, 1979), and therefore its clearance is liver dependent. Several other drugs or compounds have been reported to influence the elimination of theophylline independently of any disease state. Cimetidine (Roberts *et al.*, 1981) and propranolol (Conrad & Nyman, 1980) reduce, and smoking (Hunt *et al.*, 1976) increases it. These agents are either inhibitors or inducers (smoke) of the mixed function oxidase system in the liver. It has been suggested that macrolide antibiotics also reduce the capacity of this system (Weinberger *et al.*, 1977) and especially erythromycin and troleandomycin block one pathway of theophylline metabolism in the system in rabbits (Hemsworth & Renton, 1981). Since all these substances influence the oxidase system and have been shown to affect the elimination of theophylline, it is tempting to suggest that this system is the site of the interaction. Although we cannot confirm this suggestion from our results it seems compatible with the reduction in two major urine metabolites of theophylline after erythromycin treatment reported by Renton *et al.* (1981). However, Branigan *et al.* (1981) found no change in the pattern of theophylline metabolites in the presence of erythromycin. Plasma protein binding competitive displacement by the two drugs could be another contributing factor to the change in elimination of theophylline, although our data provide no conclusive evidence for this.

The simultaneous, theophylline-induced significant reduction in erythromycin steady state levels was the novel finding of the present study. Although the measured 'primary' pharmacokinetic parameters

absorption rate constant, ratio of unbound of total drug and the 'secondary' parameters such as elimination rate constant, and elimination half-life did not demonstrate a significant change, the 'derived' values, such as the area under the curve (within the dosing interval at the plateau) showed remarkable suppression following a uniform pattern in all directions. This suggests a change in the extent of absorption or distribution and/or elimination (in the case predominantly hepatic clearance), several factors could contribute in these changes. Theophylline induced alterations in physiological variables such as increase in secretion of acid and pepsin (Krasnow & Grossman, 1949; Debas *et al.*, 1971) and transient suppression of intestinal motility (Rall, 1980) could either inactivate the acid-sensitive erythromycin in the stomach or prevent its absorption in the intestine. Competitive displacement in plasma and/or tissue binding could explain alterations in distribution in the presence of theophylline, considering that both are more than 55% (May *et al.*, 1982) protein bound basic drugs. However, we did

not detect any significant change in plasma erythromycin protein binding. Because erythromycin is predominantly excreted unmetabolized into the bile and is a protein bound drug, liver blood flow and changes in binding brought about by theophylline, could influence its elimination. Having excluded changes in protein binding we speculate that an increase in liver blood flow induced by theophylline (Rall, 1980) might have facilitated the elimination of the antibiotic.

The present data, independent of any disease state or smoking (values from the only smoker of the study were well within the medium range), but dependent on the conditions of the study (route and duration of treatment), indicate that the pharmacokinetic interaction affects both competitors, and is a mutual interaction.

We conclude that during concurrent treatment with theophylline and erythromycin not only could theophylline concentrations reach toxic levels but also erythromycin levels could fall to subtherapeutic concentrations with serious clinical consequences.

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