Lack of Clinically Important Interaction Between Erythromycin and Theophylline

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Summary. In 11 healthy volunteers the kinetics of theophylline and the plasma levels and the urinary excretion of its metabolites were studied before and after treatment with erythromycin for 10 days. Theophylline was administered as an intravenous bolus injection (280 mg) followed by a constant intravenous infusion (23.8 ± 4.1 mg/h) for 6 hours. The total clearance of theophylline at steady-state (63.4 ± 9.9 vs 63.8 ± 14.4 ml/min, before vs after erythromycin treatment) and the elimination half-life after cessation of the infusion (6.7 ± 2.6 vs 7.5 ± 1.8 h, before vs after treatment) did not change during the treatment with erythromycin. No difference in the formation of metabolites before and after treatment with erythromycin was detected; the findings in urine were 40.4 ± 5.0 vs 42.1 ± 5.4% a,3-dimethyluric acid, 29.6 ± 4.6 vs 30.1 ± 5.9% 1-methyluric acid and 13.4 ± 3.5 vs 12.5 ± 2.2% 3-methylxanthine before and after erythromycin treatment, respectively. It is concluded that a clinically relevant interaction between erythromycin and theophylline does not occur.

Key words: theophylline, erythromycin; interaction, metabolism, pharmacokinetics

The possibility of an interaction between erythromycin and theophylline has been investigated by several authors [4, 9, 11, 12, 13, 17]. Prolongation of the elimination half-life of theophylline after pretreatment with erythromycin for 7 to 10 days was found by some authors [4, 12, 13, 17], whereas others could not demonstrate a significant change in half-life [11] or total body clearance [9]. Impairment of theophylline metabolism by erythromycin has been assumed to be the mechanism of the interaction. This assumption was based on the finding that troleandomycin, another macrolide antibiotic, inhibited the formation of one of the metabolites of theophylline (1-methyluric acid) in rabbits [7]. Since data on the metabolism of theophylline in man after pretreatment with erythromycin are incomplete, the present study was undertaken (1) to investigate the formation of theophylline metabolites, and (2) to determine the total clearance and elimination half-life of theophylline before and after treatment with erythromycin for 10 days. To achieve both aims the measurements were made under steady-state conditions for theophylline maintained for several hours by a constant intravenous infusion.

Materials and Methods

Study Protocol

The study was carried out in 11 healthy volunteers, 8 males and 3 females, aged 21–35 years, who had given their informed consent to participation in the study. 2 days prior and throughout each theophylline treatment and sampling period the volunteers abstained from dietary methylxanthines (e.g. coffee, tea, Cola, chocolate, cacao, chocolate containing cakes). No other medication was permitted from 14 days prior to the study. None of the females were taking oral contraceptives.

An i.v. bolus of 280 mg theophylline followed by a constant infusion of 23.8 ± 4.1 mg/h for 6 h (administered by means of a calibrated infusion pump, Perfusor, Braun Melsungen, FRG) was given on two occasions – before, as a control trial, and on the 10th day of erythromycin treatment. Erythromycin 4 × 250 mg was given orally (corresponding to
4 x 416.66 mg erythromycin stearate, Erythrocin®, Abbott) for 10 days. The last dose was administered i.v. at the same time as the theophylline infusion was being administered (447.7 mg erythromycin lactobionate, Erythrocin®-IV, Abbott, corresponding to 300 mg erythromycin).

Blood samples for quantitation of theophylline and its metabolites were taken 0.25, 0.5, 0.75, 1, 1.5, 2, 3.5, 5, 6, 8, 12, 16, 24 and 30 h after the start of each theophylline infusion. Urine was collected from 0–1, 1–2, 2–3.5, 3.5–5, 5–6, 6–8, 8–12, 12–16, 16–24, 24–30, 30–36, 36–48 and 48–54 h.

**Assay**

Theophylline and its metabolites, 1,3-dimethyluric acid (1,3-DMU), 1-methyluric acid (1-MU) and 3-methylxanthine (3-MX) in plasma and urine were measured using a modification of the HPLC method described by Tang-Liu et al. [15].

**Data Analysis**

**Theophylline.** Total body clearance of theophylline during the infusion period was calculated in a model-independent way from the infusion rate divided by the mean concentration during steady state (C_{ss}). Steady state was defined as the time period during which the plasma concentration did not change by more than 10%. In addition, plasma data for theophylline were fitted to an open one compartment model and β (after cessation of the infusion), AUC_{0-∞} and MRT (mean residence time) were estimated by means of the TOPFIT program [6]. Volume of distribution at steady-state (V_{ds}) was calculated by the method of Benet and Galeazzi [1] as

\[ V_{ds} = \frac{(\text{Dose}^+ / AUC_{0-∞}) \times \text{MRT}}{(\Delta U / \Delta t) / C_{ss}} \]

\( \Delta U / \Delta t \) = mean urinary excretion rate within the infusion period.

**1,3-DMU and 1-MU.** Renal clearance of 1,3-DMU and 1-MU was calculated in the same way as for theophylline. The cumulative amount excreted was determined and expressed as a fraction (f_{e} (m)) of the total amount of unchanged and changed drug recovered in urine. Clearance to the metabolite (Cl_{met}) was calculated according to

\[ Cl_{met} = f_{e} (m) \times Cl_{tot} [5] \]

**Metabolites**

Mean kinetic parameters of the metabolites are summarized in Table 2.

1,3-DMU. Steady-state levels of 1,3-DMU were reached within 1 to 2 hours after the start of the infusion (Fig. 1). The mean plasma level at steady-state and the renal clearance of this metabolite were not altered by erythromycin pretreatment (Table 2). Thus, as a steady-state condition was present, the urinary excretion rate (\( \Delta U / \Delta t \)) could be regarded as the metabolite formation rate. There was no change in the rate of metabolite formation (8.3 ± 4.3 mg/h vs 8.0 ± 4.0 mg/h, control vs erythromycin trial, respectively) or in Cl_{met} (Table 2).

1-MU. Steady-state plasma levels of 1-MU were reached within 1 to 2 hours after the start of the infusion. They were lower in 9 out of 11 volunteers after pretreatment with erythromycin (Table 2), but the difference was not significant. The renal clearance of the metabolite was found to be consistently higher when erythromycin was given concomitantly, the mean values being 278.2 ± 167.6 ml/min and 494.7 ± 256.7 ml/min without and with erythromycin.