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Predicting the ciprofloxacin-theophylline interaction from single plasma theophylline measurements

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The effect of ciprofloxacin treatment on theophylline clearance was evaluated with a theophylline multiple dose, multiple sample protocol and with a single dose, single sample protocol. The object was to determine whether a single dose, single sample protocol for estimating theophylline clearance could be used as a screening strategy for evaluating host factor influences on theophylline clearance. Ciprofloxacin (750 mg *per os*) was administered every 12 h for nine doses in the multidose study and every 12 h for seven doses in the single dose protocol. Subjects were sixteen healthy, non-smoking young adult males. The oral clearance of theophylline at steady state, $(CL/F)_{ss}$, decreased from a mean (± s.d.) value of 0.035 (± 0.008) 1 h^{-1} kg^{-1} to 0.024 (± 0.004) 1 h^{-1} kg^{-1} during ciprofloxacin treatment. Single sample estimates of theophylline clearance, CL/F, similarly decreased from 0.040 (± 0.014) 1 h^{-1} kg^{-1} to 0.018 (± 0.008) 1 h^{-1} kg^{-1}. Mean theophylline clearances were significantly different when comparing control with ciprofloxacin treatment means ($P< 0.01$), but were not different when comparing single sample *vs* multiple sample clearances for a given treatment (i.e. control or ciprofloxacin). It is concluded that a single dose, single sample strategy may be used in screening for host-factor influences on theophylline clearance.

Keywords ciprofloxacin theophylline clearance interaction

Introduction

The ability of fluoroquinolones to slow theophylline clearance is well known. The effect of enoxacin is most dramatic, with a 64% decrease in theophylline clearance reported among patients with chronic obstructive lung disease (Wijnands *et al.*, 1986). These investigators also reported that theophylline clearance was approximately one-third lower among patients concomitantly treated with theophylline and either ciprofloxacin or pefloxacin compared with theophylline only (Wijnands *et al.*, 1986). Our findings regarding the interaction between theophylline and ciprofloxacin corroborate those of Wijnands' group (Schwartz *et al.*, 1988). Conditions which permit the use of theophylline as a single dose, single sample probe of host factor influences on drug metabolism have been reported previously (Bachmann *et al.*, 1985b). Having investigated the interaction between ciprofloxacin and theophylline using a conventional multiple dose, multisample protocol (Schwartz *et al.*, 1988), we wished to determine whether the same information could be obtained from a scaled-down protocol employing only a single low dose of theophylline and the measurement of a single plasma drug concentration in each subject.

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Methods

Sixteen healthy, non-smoking male volunteers ranging in age from 21–36 years and weighing 67.7–88.5 kg participated after giving written, informed consent. Six subjects participated in the multiple dose protocol only, seven subjects participated in the single dose protocol only, and three subjects participated in both protocols. Ten weeks elapsed between the multiple dose and single dose protocols. Subjects underwent a physical examination and routine laboratory tests of blood and urine prior to participating. One subject who was taking ranitidine chronically was allowed to participate since eight controlled studies have demonstrated no influence of ranitidine on theophylline kinetics (Mitchard *et al.*, 1987). All others were drug-free, and abstained from alcohol and methylxanthine-containing foods and beverages, beginning at least 24 h prior to each study period. The multiple dose protocol has been described in detail elsewhere (Schwartz *et al.*, 1988), and is summarized here. A 200 mg sustained-release theophylline tablet (Theodur; Key Pharmaceuticals) was administered orally every 12 h for 10 days. The morning dose was ingested with 180 ml of tap water after a 10 h fast, and food was withheld for another 4 h. The evening dose was ingested in the same manner approximately 2 h after a standardized meal. Ciprofloxacin (Miles Pharmaceuticals, West Haven, Connecticut) was taken orally in 750 mg doses every 12 h along with theophylline on study days 4, 5, 6, and 7 and on the morning of study day 8. Blood (5 ml) was collected by venepuncture immediately prior to each theophylline dose. On days 3, 6, 8 and 10 samples were collected at the following times: 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 12 h post dose. Serum was collected, and stored at –20°C. The single dose protocol was performed as a two-way cross-over as follows: Ten subjects were randomly allocated into two groups of five subjects each. Subjects in Group A received a single 2 mg kg^{-1} oral dose of theophylline (Slo-Phyllin Syrup, Wm. H. Rorer, Inc., Ft. Washington, Pennsylvania). Group B subjects also ingested a single 2 mg kg^{-1} oral dose of theophylline, however their dose was taken concomitantly with the seventh and last dose of an oral ciprofloxacin regimen (750 mg every 12 h). Theophylline was ingested with 180 ml of tap water after a 10 h fast, and food was withheld for another 2 h. Blood (5 ml) was collected by venepuncture 12 h after the theophylline dose. Plasma was collected and stored at –20°C. Four days after the ingestion of theophylline subjects were crossed over, and those in Group A began a seven dose regimen of ciprofloxacin (750 mg every 12 h) while subjects in Group B remained drug free. One week after ingestion of the first single 2 mg kg^{-1} dose of theophylline each subject ingested a second single 2 mg kg^{-1} dose, and a blood sample was again collected 12 h later.

Thawed serum and plasma samples were vortexed for 2 s. Aliquots (100 μl) were then analyzed for theophylline by fluorescence polarization immunoassay (FPIA) using a TDx analyzer (Abbott Laboratories, Irving, Texas) and commercially available reagent kits. FPIA has been described by Dandliker & Kelly (1973) and Jolley (1981). Samples were assayed in duplicate.

Oral clearances of theophylline at steady-state were estimated for the multiple dose, multi-sample protocol on study days 3, 6, 8, and 10; prior to ciprofloxacin treatment, during the third and fifth days of ciprofloxacin treatment, and two days after terminating ciprofloxacin treatment, respectively. The following relationship was used:

$$(CL/F)_{ss} = D/AUC_{\tau} \quad (1)$$

where CL is the clearance of theophylline, F is the fraction of the dose absorbed, D, and AUC is the area under the plasma drug concentration *vs* time curve during a dosing interval, τ, at steady-state. AUC was estimated by the trapezoidal rule.

Single sample oral theophylline clearances were estimated from theophylline concentrations drawn 12 h after a single 2 mg kg^{-1} theophylline dose as follows:

$$CL/F = [\ln(D/V) - \ln C(12) \bullet V/t \quad (2)$$

where $C(12)$ is the 12 h post dose plasma theophylline concentration, V is a population mean value for theophylline volume of distribution set at 0.5 l kg^{-1}, and t is the post dose sampling time of 12 h.

Differences between mean oral theophylline clearances for the multiple dose protocol were assessed with one-way ANOVA and the Tukey method (see Schwartz *et al.*, 1988). Differences between mean oral theophylline clearances for the single dose protocol were analyzed initially by a two-way ANOVA. Since this analysis revealed no significant differences within either treatment (control or ciprofloxacin) arising from the order in which the treatment was administered, all ten variates within each treatment were subsequently pooled. Differences between mean oral clearances for both protocols were then assessed by a one-way ANOVA and the Tukey method. For this comparison only the day

3 and day 8 theophylline clearances in the multidose study were used since the day 3 clearance was pre-ciprofloxacin and on day 8 the effect of ciprofloxacin was greatest. Differences were considered significant at $P<0.05$.

Results

The coefficient of variation for the assay of theophylline was 3.7%, and the sensitivity limit was 0.5 mg l^{-1}. One of the subjects in the multiple dose protocol withdrew from the study prior to the fifth day of concomitant ciprofloxacin and theophylline dosing owing to the appearance of flu-like symptoms.

In the multidose study the mean (± s.d.) control (i.e. pre-ciprofloxacin) steady-state oral theophylline clearance $(CL/F)_{ss}$ was 0.035 (± 0.08) 1 h^{-1} kg^{-1}, and it decreased on the fifth day of concomitant ciprofloxacin use (study day 8) to 0.024 (± 0.004) 1 h^{-1} kg^{-1} ($P<0.001$).

In the single dose, single sample study the control theophylline clearance estimate, CL/F, was 0.040 (± 0.014) 1 h^{-1} kg^{-1}. After seven doses of ciprofloxacin oral theophylline clearance decreased to 0.018 (± 0.008) 1 h^{-1} kg^{-1}. Clearances for both multiple dose and single dose protocols are shown in Figure 1. ANOVA and the Tukey method revealed that significant differences existed between control and treatment means ($P<0.01$), but not between multiple dose *vs* single dose control clearances or between multiple dose *vs* single dose theophylline clearances during ciprofloxacin treatment.

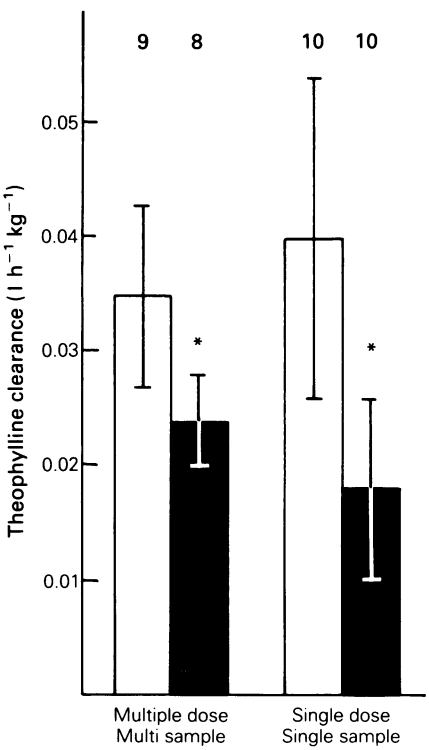

Figure 1 The effect of ciprofloxacin treatment on estimates of theophylline clearance. Bars depict clearance means. Vertical lines depict ± 1 s.d. of the mean. Open bars represent mean theophylline clearances in the absence of ciprofloxacin treatment, and closed bars represent clearance means during ciprofloxacin treatment. Asterisks denote significant differences between treatment (control *vs* ciprofloxacin) means, $P<0.01$. Numbers atop bars denote the number of subjects, *n*.

Discussion

Both the multiple dose and single dose, single sample protocols for investigating the influence of concomitant ciprofloxacin treatment on theophylline clearance revealed that ciprofloxacin treatment can significantly decrease theophylline clearance. Both approaches yielded results that are consistent with other reports of this interaction. Nix *et al.* (1987) reported that ciprofloxacin decreased theophylline clearance from control values of *circa* 4 l h^{-1} by only 18% ($P<0.1$). However, three of their eight subjects were cigarette smokers. They noted that among three of their subjects theophylline clearance was decreased between 42 and 113% by ciprofloxacin. Wijnands *et al.* (1986) reported a more marked effect of ciprofloxacin among patients with chronic obstructive lung disease who were treated with theophylline. They found a 30% decrease in theophylline clearance among eight such patients whose control theophylline clearances averaged *circa* 5 l h^{-1}. Our multiple dose study as outlined above and described in detail elsewhere (Schwartz *et al.*, 1988) yielded results that are in close agreement with the findings of Wijnands *et al.* (1986), *viz.* a ciprofloxacin-induced 31% decrease in apparent steady-state theophylline clearance among healthy, young adult males.

Raoof *et al.* (1987) recently reported ciprofloxacin-induced increases in serum theophylline concentrations among in-patients with respiratory tract infections. The mean increase in serum theophylline concentrations during ciprofloxacin treatment was 57%. Assuming that the serum theophylline measurements were all made at steady-state, that the samples for any patient were drawn at comparable times within dosing intervals, and that each patient's condition was stable throughout the sampling

period, it may be inferred that ciprofloxacin treatment produced a comparable decrease in the steady-state clearance of theophylline. The range of serum theophylline increases in the report of Raoof *et al.* (1987) was from 28 to 1000%.

The single dose, single sample strategy for evaluating host factor influences on the clearance of antipyrine was described by Dossing *et al.* (1982). Since then other drugs whose clearances can be estimated by a single dose, single sample protocol as well as the conditions permitting such estimations have been identified. Among these drugs are amylobarbitone (Bachmann, 1987), ethosuximide (Bachmann *et al.*, 1987), phenytoin (Bachmann *et al.*, 1985a) and theophylline (Bachmann *et al.*, 1985b). Both theophylline and phenytoin exhibit nonlinear pharmacokinetics, but account has been taken of that characteristic in terms of both the doses and sampling times used in the single dose, single sample estimates of their clearances. There are other limitations to the use of a single plasma concentration measurement of drug after a single dose for estimating clearance which have been discussed previously (Bachmann, 1987; Bachmann *et al.*, 1985a, b, 1987).

When applied to the study of the interaction between theophylline and the fluoroquinolone antibacterial drug, ciprofloxacin, a single dose, single sample strategy produced results comparable with those derived from more exhaustive multiple dose studies of the interaction. While we do not recommend such a single dose, single sample strategy as an alternative to more conventional pharmacokinetic studies of drug interactions, it does appear that for some drugs the single dose, single sample approach can serve as a useful screening tool for the preliminary evaluation of host-factor influences on clearance.

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