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Assessment of pharmacokinetic interaction between theophylline and loperamide in the rat

A. TEKLE, S.A. BAWAZIR, M.I. Al - HASSAN AND K.M. MATAR

Department of Clinical Pharmacy
College of Pharmacy, King Saud University
Riyadh, Saudi Arabia

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SUMMARY

The effect of loparamide (1 $mgkg^{-1}$, p.o.) on the pharma-cokinetics of theophylline was studied in the rat. Theophylline (as aminophylline - 25 $mgkg^{-1}$, p.o.) was administered either alone, in combination with, or 1 hr after loperamide. Plasma levels of theophylline were serially measured over a period of 12 hr using HPLC. The disposition kinetics of theophylline was markedly altered by loperamide. This was evident from the significant differences obtained between the control and drug combination groups in most of the parameters studied (Cpmax, tmax, Ka, t1/2 and AUC). Allowing for the limitations of single dose studies, the data presented here suggest that pharma - cokinetic interaction between theophylline and loperamide is possible during their comcomitant use.

INTRODUCTION

Loperamide is a synthtic opiate analogue of the piperidine class that is widely used in the treatment of diarrhea (1). It has potent inhibitory action on gastrointestinal motility and gastric secretion (2.3). Following its recent classification as an over-the-counter (OTC) product, loperamide has rapidly supplanted the conventional preparations in the management of diarrhea associated with a variety of disease states. It may, for example, be effectively used to control diarrheal episodes in patients with underlying chronic obstructive lung diseases. In such clinical conditions, drug therapy could involve the coadministration of loperamide with a bronchodilator substance such as theophylline.

The concomittant use of loperamide and theophylline may, however, precipitate a pharmacokinetic drug interaction that could adversely affect the primary drug therapy. The absorption profile of theophylline may indeed be altered by loperamide induced changes in the functional tone of the gastrointestine. Moreover, a substantial portion of orally administered dose of loperamide is biotransformed in the liver prior to its excretion (5). Interaction with theophylline is therefore possible at the level of oxidative metabolic processes which also feature extensively during theophylline clearance (6).

We report here a study in the rat, designed to examine the potential interaction between these drugs at the various phases of drug disposition. The pharmacokinetic profiles of theophylline when administered alone and in combination with a single dose of loperamide are compared to assess the interaction. A study of the disposition parameters of the drug in loperamide pretreated aminals (the doses of theophylline and loperamide were separated by 1 hr) is also included to examine the importance of dose proximity in the interaction.

Send reprint requests to: Dr. A. Tekle, Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

MATERIALS AND METHODS

Animal Preparation and Sample Collection

Adult male Wistar rats weighing between 300-350 g were used in the study. The animals were fasted overnight (water ad libtum) and randomly assigned to treatment groups (n = 10). The right femural artery was cannulated (7) and the drug(s) administered as follows:

theophylline (25 $mgkg^{-1}$, p.o.) alone; concurrently with, and following 1 hr pretreatment with loperamide (1.0 $mgkg^{-1}$, p.o.). The drugs (theophylline ethylene diamine and loperamide hydrochloride) were administered in normal saline at a constant volume of 1 $mlkg^{-1}$. Blood (ca. 0.3ml) samples were collected into heparinized Eppendorff tubes prior to and then serially at 15, 30, 60 min and 2, 3, 4, 6, 8, 10 and 12 hr. following theophylline administration. The samples were then immediately centrifuged and the plasma stored at -20°C until drug assay.

Drug Analysis:

Prior to the chromatographic analysis, sample preparation involved the precipitation of plasma proteins with acetonitrile. To 100 µl of plasma were added 100 µl of acetonitrile (containing the internal standard - caffeine) and the contents vortex - mixed for 2 min. The mixture was then centrifuged at 4000 xg for 15 min. From the resulting supernatant aliquots of 20 µl were applied to the chromatograph which consisted of a Waters HPLC system (Waters Associate, Milford, M.A.) equipped with a solvent delivery system (M. 45), sample processor (WISP - 71 0B), a system controller (M-720), a data module (M-730) and a variable wavelength UV detector (M-481). The samples were run on a µ-Bondapack C18 column (10µ, 10cm x 8 mm, i.d.) used in conjunction with a Z module radial compression system. Acetonitrile -phosphate (0.01 M, K_2HPO_4) buffer mixture (8:92 v/v) at pH 6 and a flow rate of 4 ml min^{-1} was used as the mobile phase. The effluent was monitored at 280 nm. Under these conditions the retention times of theophylline and the internal standard, were 4.5 and 8.6 min, respectively. Plasma theophylline concentration was quantified using peak height ratios from a calibration curve prepared on the day of sample assay.

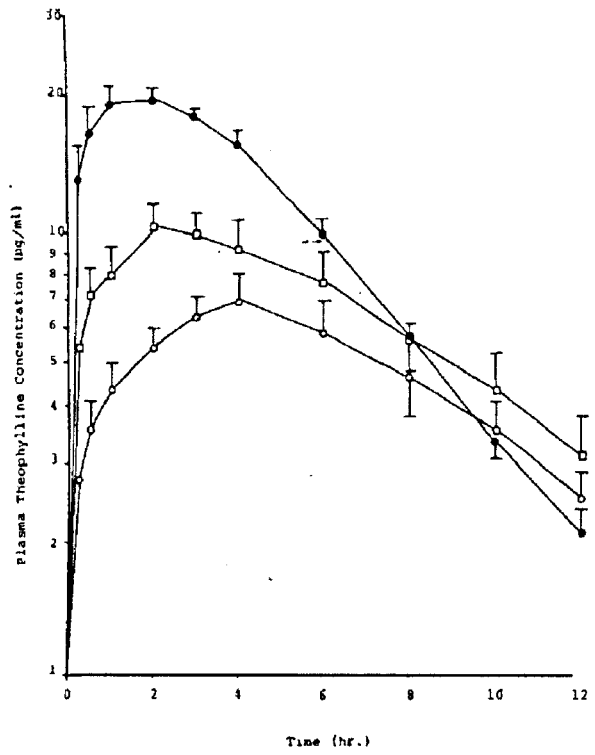

Fig. 1 Mean (±SEM) plasma theophylline concentration - time profile when (●) administered alone (25 $mgkg^{-1}$); (o), concurrentrly with loperamide (1 $mgkg^{-1}$, p.o.) and (□) after 1 hr pretreatment with loperamide.

Data Analysis:

Individual plasma theophylline concentration - time data were fitted to a first order single compartment open model and the peak plasma level (Cp_{max}) and the time at which this was attained (t_{max}) were determined by graphical inspection. The absorption rate constant (Ka) was determined by the method of residuals. The elimination half - life ($t_{1/2}$) was derived from the elimination rate constant (Kel), first obtained from the slope of the terminal log-linear portion of the plasma concentration - time curve by the method of least square regression analysis. The area under the plasma concentration - time curve (AUC) was computed by means of the trapezoidal rule. Differences in the values of the various pharmacokinetic parameters between treatment groups were statistically evaluated using a two tailed Student t-test with a probability (P) value of 0.05 or less taken as significant. All values are reported as the mean ±SEM.

RESULTS

Fig. 1 shows the plasma concentration profile of theophylline under the three dosing schedules: theophylline alone (control); concurrent with, and after 1hr loperamide pretreatment, respectively. The pharmacokinetic parameters (Cp_{max}, t_{max}, Ka, $t_{1/2}$, AUC_{0-12} and $AUC_{0-\infty}$) derived from the data in each schedule are listed in Table I.

In the control group, plasma theophylline concentration increased rapidly reaching a maximum value of 21.39 ± 0.85 μgml^{-1} after 1.45 ± 0.28 hr from oral administration. The inclusion of loperamide in the

Table I: Computed mean pharmacokinetic parameters for oral theophylline alone (25 $mgkg^{-1}$) and in combination with (1 $mgkg^{-1}$) Loperamide (n=10).

Pharmacokinetic Parameter	MEAN (±SEM)		
	Theophylline alone (control)	Theophylline with loepramide	Theophylline after loperamide
Cp_{max} ($mgml^{-1}$)	21.39 ± 0.85	9.44 ± 0.95*	10.83 ± 1.25*
t_{max} (hr.)	1.45 ± 0.28	3.25 ± 0.39*	2.73 ± 0.29*
$t_{1/2}$ (hr.)	2.68 ± 0.18	5.71 ± 0.75*	5.02 ± 0.50*
Ka ($hr.^{-1}$)	0.87 ± 0.03	0.63 ± 0.01*	0.39 ± 11.49*
AUC_{0-12} ($mg\ hr.ml^{-1}$)	123.31 ± 5.18	56.91 ± 7.54*	81.29 ± 11.4 9*
$AUC_{0-\infty}$) ($mg\ hr.ml^{-1}$)	131.68 ± 6.26	76.50 ± 8.41*	106.17 ± 17. 95*

*Significantly different from control.

theophylline dose regimen significantly altered the absorption profile of the drug. A peak theophylline concentration of 9.44 ± 0.95 μgml^{-1} was attained at 3.25 ± 0.39 hr during coadministration. The corresponding values in the pretreated group were 10.83 ± 1.25 μgml^{-1} and 2.73 ± 0.29 hr, respectively. The effect of loperamide on the rate of theophylline absorption was readily apparent from the significant differences observed in the absorption rate constants (Ka) for the different schedules. Within the two loperamide treatment categories, theophylline levels were higher in the pretreatment schedule at all time points but the difference was not of sufficient magnitude to be reflected in significant differences in the respective AUC's. The elimination half - life was comparable in both treatment categories. Compared to control, the loperamide treated groups showed significant differences in most of the pharmacokinetic parameters considered (see Table I).

DISCUSSION

The inhibitory influence of loperamide on gastric and small bowel peristaltic activity manifests in increased gastrointestinal transit time (GITT), one of the major determinants of drug absorption (1).

Data presented here show that loperamide interferes with the disposition kinetics of theophylline. Expressed as a ratio of treatment AUC to control, theophylline bioavailability was reduced by over 50% during coadministration. The depression of theophylline levels in plasma was substantially attenuated when the doses of the drugs were separated by 1 hr.

In the rat, peak plasma level (and presumably peak drug effect) of loperamide occurs at about 1 hr following oral administration (8). The marked reduction in theophylline absorption seen during concurrent administration and the attenuation of this effect by separating the doses suggest that both specific and non specific drug effects may be involved in the interaction. Alteration in the rate of drug absorption may result from loperamide induced inhibition of gastric motility which slows the passage of orally administrered theophylline to the upper small intestine, the principal site of drug absorption. Loperamide may also elevate the gastric pH thereby promoting ionization of the compound (9). This could effectively reduce the concentration of absorbable, unionized drug species. Physical incompatibility between these agents was not observed during in vitro mixing, but its occurrance cannot be ruled out in the gastric mileu.

The coadministration of loperamide with theophylline was also associated with significant changes in the elimination half -life and area uner the curve indicating a possible interaction at higher levels beyond the absorption phase. The pattern of concentration decay in the drug combination schedules may suggest a role for displacement interaction at the level of drug binding to plasma proteins. The extent of loperamide binding to these sites is, however, much lower than that for theophylline (8) and the significance of this mechanism for the observed interaction is bound to be minimal. Metabolic interaction at the hepatic level may, however, be a very likely mechanism since both loperamide and theophylline undergo microsomal N-demethylation and oxidative dealkylation during their biotransformation (5,6).

Previous studies on the influence of antimotility

agents on the disposition characteristics of coadministered drugs are few and varied. Increased drug absorption from prolongation of gastrointestinal transit time was reported with diphenoxylate (10) but this effect was not readily apparent with loperamide (11, 12).

The results of the present study do not relate favourably to these reports. They point instead, to a marked interaction that depresses both the rate and extent of coadministered drug. Furthermore, the proximity of the loperamide dose to the administration time of theophylline appears to be important in the drug interaction. Although the clinical significance of this observation has yet to be fully assessed in more appropriate subjects, the data in the present study may serve as a preliminary indicator to the potential interaction that can exist when using these two drugs.

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