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THE EFFECT OF DOMPERIDONE ON THEOPHYLLINE DISPOSITION IN THE RAT

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ABSTRACT

The effect of domperidone (2 mg kg^{-1}) on the pharmacokinetics of a single oral dose of theophylline (25 mg kg^{-1}) was studied in the rat. Theophylline concentrations were measured serially for 12 h using an HPLC technique. Domperidone did not have any significant effect on any of the four parameters studied: peak plasma levels (Cp_{max}), the time these were attained (t_{max}), elimination half-life ($t_{1/2}$) and area under the plasma concentration–time curve (AUC). Our data preliminarily suggests that domperidone may be safely coadministered with theophylline but clearly further studies in patients or relevant animal models of gastric motility disturbances are needed to reliably rule out any potential interaction between these agents.

KEY WORDS Domperidone Theophylline Pharmacokinetic interaction

INTRODUCTION

Theophylline is an effective bronchodilator frequently prescribed in the treatment of patients with chronic obstructive lung disease.[1] The drug is characterized by a fairly narrow therapeutic range, 10 to 20 $\mu g\ ml^{-1}$, and wide interindividual variation in plasma levels following standardized doses. Furthermore, the disposition kinetics of theophylline are known to be markedly influenced by diverse factors such as cigarette smoking, dietary manipulations, hepatic cirrhosis, and the concomitant use of various drugs.[2] Often, serum theophylline levels need to be routinely monitored to optimize and individualize the therapeutic benefit especially when the drug is being given in combination with other agents. One such agent may be domperidone, the specific peripheral dopamine receptor antagonist with potent antiemetic and gastrostimulant activity.[3]

Like theophylline, domperidone is highly bound to plasma proteins and is also extensively metabolized by the mixed-function oxidase enzyme system in liver microsomes.[4] Therefore, concurrent administration of these agents for a variety of clinical conditions may result in drug interaction.

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We report here a study in the rat, aimed at examining the potential for such an interaction, through studying the effect of domperidone on the disposition kinetics of orally coadministered theophylline.

MATERIALS AND METHODS

Animal surgery and sample collection

Male albino rats of Wistar origin weighing 300 to 350 g were used in the study. After an overnight fast (water given *ad libitum*) the right femoral artery was cannulated, under light ether anaesthesia, with a segment of heparinized polyethylene tubing (PE-50, Jencons Scientific Ltd, Beds). The patented cannula was pulled under the skin and positioned at the back of the neck to facilitate subsequent blood sampling. Following the surgical procedures, the animals were placed in specially adapted rat restrainer cages and allowed to recover from anaesthesia before oral dosing with the appropriate drug or drug combination. Theophylline (25 mg kg^{-1}) was given as its ethylene diamine derivative (Aminophylline) dissolved in normal saline and domperidone (2 mg kg^{-1}) was administered as a suspension in 1 per cent carboxymethyl cellulose. Each treatment category had 10 rats. Blood (0·5 ml) was serially withdrawn via the indwelling cannula into small heparinized Eppendorff tubes at 0, 15, and 30 min, 1, 2, 3, and 12 h from drug administration. Each sample withdrawal was compensated by flushing in an equal volume of normal saline via the cannula. The blood samples were immediately centrifuged and 100 μl aliquots of plasma were stored at –20° for subsequent assay.

Drug analysis

The plasma samples were first thoroughly mixed with 100 μl of acetonitrile (containing the internal standard — caffeine) to precipitate plasma proteins, and subsequently centrifuged at 4000 × g for 15 min. From the resulting supernatant, aliquots of 20 μl were sampled for chromatographic assay. The assay involved a reversed phase HPLC technique employing a Waters Associates Chromatograph equipped with a sample processor (WISP-710B), 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 C_{18} cartridge column (10 μm 10 cm × 8 mm, i.d.) with a mixture of acetonitrile and phosphate buffer (0.01M) 8:92 v/v, adjusted to pH 6·0, as the mobile phase. The effluent was monitored at 280 nm with flow rate set at 4 ml min^{-1}.

Data analysis

Peak plasma concentrations (C_{pmax}) and the times at which these were reached, were obtained by graphical inspection. The elimination rate constant (k_{el}) was determined by linear regression analysis of the plasma concentration–time data

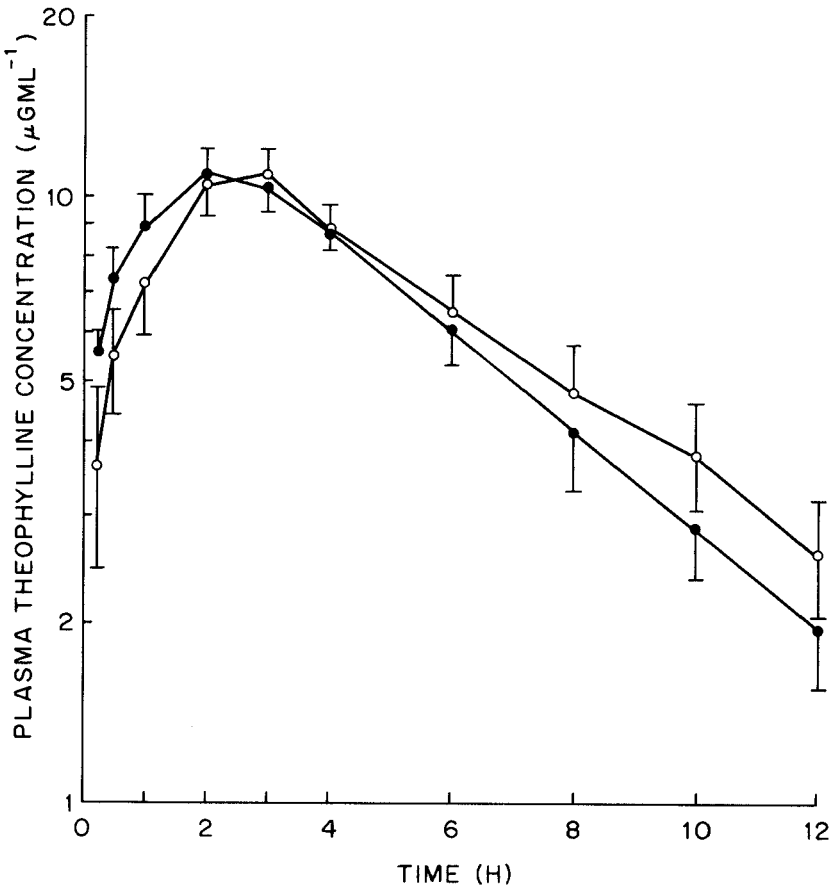

Figure 1. Mean (±SEM) plasma concentration – time profile of theophylline (25 mg kg^{-1} p,o) alone (—•—) and in combination (—o—) with 2 mg kg^{-1} domperidone (n=10)

of the terminal phase. Elimination half-lives ($t_{1/2}$) were calculated from the terminal log-linear portions of the plasma concentration–time curve. The area under the plasma concentration–time curve (AUC) was computed by means of the trapezoidal rule. The significance of the difference between the groups was evaluated by using the Student's t-test with a probability (p) value of 0·05 or less taken as significant. All values are reported as the mean ± SEM.

RESULTS

The mean plasma concentrations of theophylline at each time point following administration of the drug (25 mg kg^{-1}P.O) alone or in combination with domperidone (2 mg kg^{-1}P.O) are shown in Figure 1. The data fitted a single-

Table 1. Mean (±SEM) computed parameters for theophylline (25 mg kg^{-1}) administered alone or in combination with domperidone (2 mg kg^{-1})

Parameter	Mean + SEM (n = 10)		Statistics (t-test)
	Alone	With domperidone	
AUC up to 12 h (μg h ml^{-1})	73·10±5·27	75·50± 9·90	NS
AUC up to infinity (μgh ml^{-1})	84·90±7·50	95·40±14·80	NS
Maximum conc. (C_{pmax}, $\mu g ml^{-1}$)	12·62±0·86	11·37± 1·32	NS
Time to max. conc. (T_{max} h.)	2·56±0·47	2·80± 0·15	NS
Elimination half-life ($t_{1/2}$ h)	3·66±0·47	4·62± 0·55	NS

NS: Non-significant, ($p > 0·05$).

compartment open model with first order kinetics and the pharmacokinetic parameters derived from this data are listed in Table 1.

In both treatment categories, absorption proceeded fairly rapidly with maximum concentrations occurring at 2·56±0·47 and 2·8±0·15 h for the single and combined drug treatment groups, respectively. The corresponding peak plasma levels (C_{pmax}) were 12·62±0·86 and 11·32±1·32 $\mu g ml^{-1}$. The average values of the elimination half-lives were 3·66±0·47 and 4·26±0·55 h, respectively. Furthermore, the mean estimates of AUC both for time 0 to 12 h and 0 to infinity were very similar in both treatment categories (Table 1). All four pharmacokinetic parameters studied (C_{pmax}, t_{max}, AUC $0\text{-}\infty$, $t_{1/2}$) failed to show any significant difference between the groups.

DISCUSSION

The absorption profiles of a number of drugs have been shown to be markedly influenced by changes in gastrointestinal motility[5–7]. Domperidone with its potent gastrokinetic property (i.e. the enhancement of smooth muscle contractile activity, reduction of gastric emptying and gastrointestinal transit time) may thus alter the absorption characteristics of coadministered drugs. A reduction in the time required for an orally administered dose to reach the small intestine, the principal site of absorption, may be accompanied by changes in either the rate or extent of the drug absorbed.

Data presented here, however, indicate that domperidone concurrently given with theophylline does not alter the absorption characteristics of the latter. Both peak plasma levels (C_{pmax}) and the times these were attained (t_{max}) were not significantly affected. Furthermore, the close values for the $t_{1/2}$ and AUC obtained for theophylline under the two treatment regimes demonstrate the absence of drug interaction at the levels of plasma protein binding, metabolism and excretion. These observations are in sharp contrast to the known disposition characteristics of each individual drug, but they are nevertheless in close agreement with a previous report on the effect of metoclopramide on theophylline pharmacokinetics. None of the essential parameters of theophylline disposi-

tion was significantly altered by the concurrent administration of this potent gastrostimulant.[8] In another study, domperidone was shown to have little or no effect on the absorption profile of levodopa when the two drugs were given simultaneously to normal subjects.[9] These investigators were not, however, able to rule out the possibility of interaction due to the small sample size in their study. The apparent lack of demonstrable interaction in our study, may in part be due to the low bioavailability of orally administered domperidone. The drug is characterized by extensive first-pass elimination as a result of intestinal and hepatic metabolism.[10] Although the dose of domperidone selected for this investigation was within the therapeutic equivalent range, gut-wall metabolism of domperidone may have been further enhanced by our use of fasted subjects. Thus at low levels of gastric stimulation, drug-induced changes in the absorption and metabolic profiles of theophylline may not be fully apparent. In addition, the magnitude of the gastrostimulant effect of domperidone may be influenced by the state of the functional tone of the gastrointestinal tract of the subjects. Pathophysiological conditions of disturbed gastric motility and emptying may be more responsive to lower doses of domperidone.[11] Our results, though pointing to the absence of significant interaction between domperidone and theophylline, cannot be extrapolated to clinical situations of gastric stasis. Further studies in patients or relevant animal models may be needed to reliably exclude theophylline–domperidone interaction during their concurrent administration.

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REFERENCES

1. L. Hendeles and M. Weinberger, *Pharmacotherapy,* **3**, 2 (1983).
2. J. P. Jusko, M. J. Gardiner, A. Mangione, J. J. Schentag, J. R. Koup and J. W. Vance, *J. Pharm. Sci.,* **68**, 1358 (1979).
3. R. N. Brogden, A. A. Carmine, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs,* **24**, 360 (1982).
4. W. Meuldermans, R. Hurkmans, E. Sweysen, J. Hendricks, M. Michiels, W. Lauwers, and J. Heykants, *Eur. J. Drug Metabol. Pharmacokinet.,* **6**, 49 (1981).
5. J. Nimmo, *Postgrad. Med. J.* (Suppl. 4), **49**, 25 (1973).
6. R. C. Heading, J. Nimmo, L. F. Prescott and P. Tothill, *Br. J. Pharmacol,* **47**, 415 (1973).
7. G. N. Volans, *J. Clin. Pharmacol.,* **2**, 75 (1975).
8. R. A. Steeves, J. D. Robinson, M. W. McKenzie and P. G. Justus, *Clinical Pharmacy,* **1**, 356 (1982).
9. I. D. Bradbrook, H. C. Gillies, P. J. Morrison and H. J. Rogers, *Eur. J. Clin. Pharmacol.,* **29**, 721 (1986).
10. J. Heykants, R. Hendricks, W. Meuldermans, M. Michiels, H. Scheygrond and H. Reyntijens, *Eur. J. Drug Metabol. Pharmacokinet.,* **6**, (1), 61 (1981).
11. A. Reyntjens, *Postgrad. Med. J.* (suppl. 1), **55**: 50 (1979).