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EFFECT OF DOMPERIDONE ON CIMETIDINE AND RANITIDINE ABSORPTION IN RABBITS

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ABSTRACT

Cimetidine and ranitidine absorption were studied after oral administration to rabbits, alone or in combination with oral and intravenous domperidone. Blood samples were collected before and 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 3·0, 4·5, and 6·0 h after cimetidine and ranitidine administration. Assays of cimetidine and ranitidine in plasma samples were carried out using HPLC method. Domperidone overall significantly reduced the area under the plasma concentration–time curve (AUC) by approximately 30 per cent for both drugs. However, domperidone had little effect on the maximum plasma concentration (C_{max}), the time taken to reach the maximum plasma concentration (T_{max}), and the elimination half-life ($t_{1/2}$) of cimetidine and ranitidine. The results suggest that domperidone affects the extent but not the rate of cimetidine and ranitidine absorption by enhancing gastric emptying.

KEY WORDS Cimetidine absorption Ranitidine absorption Domperidone interaction Bioavailability Rabbits

INTRODUCTION

Domperidone is a dompamine antagonist with antiemetic properties similar to metoclopramide and certain neuroleptic drugs.[1] Unlike these drugs, however, domperidone does not readily cross the blood–brain barrier and seldom causes extrapyramidal side-effects.[2–4] Several cases of cardiac arrest and arrhythmias have been reported recently after high intravenous doses of domperidone.[5,6]

In man, changes in drug absorption have been reported for a number of drugs associated with delayed or accelerated gastric emptying.[7,8] Metoclopramide which accelerates gastric emptying, markedly reduces the bioavilability of cimetidine in man,[9] while propantheline, which decreases gastric emptying, also reduces cimetidine bioavilability.[10] Since, domperidone is as effective as metoclopramide for GI indications and cimetidine or ranitidine may be given

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together with domperidone, this study was designed to investigate whether any interaction occurs at the level of absorption in rabbits.

MATERIALS AND METHODS

Materials

Domperidone was kindly gifted by Janssen Pharmaceutica (Belgium) and ranitidine HCl by Glaxo Ltd (Hertfordshire, England). Cimetidine HCl and internal standard (SK&F 92374) was supplied by Smith Kline and French Laboratories Ltd (Hertfordshire, England). All other reagents used were spectroscopic or finer grade.

Methods

Male New Zealand white rabbits weighing 2·3 to 3·8 kg were fasted overnight prior to the experiment, but water was allowed *ad libitum*. Food and water were withheld during the first 6 hours of the experiment.

Cimetidine ($10\,mg\,kg^{-1}$) or ranitidine ($20\,mg\,kg^{-1}$) alone or in combination with domperidone ($2\,mg\,kg^{-1}$) were orally adminsitered with 20 ml of distilled water. For intravenous treatment, domperidone ($1\,mg\,kg^{-1}$) was injected through the ear vein 15 min prior to oral administration of cimetidine or ranitidine. Each rabbit received the treatment according to a randomized, three-way crossover design with a 10-day interval between treatments. Cimetidine ($40\,mg\,ml^{-1}$) syrup, ranitidine ($10\,mg\,ml^{-1}$) solution, and domperidone ($1\,mg\,ml^{-1}$) suspension were used for oral administration. Domperidone ($2\,mg\,ml^{-1}$) solution was used for i.v. administration. Blood samples (0·5 ml) were collected from the ear vein before and 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 3·0, 4·5, and 6 h after oral administration. Heparinized blood was centrifuged, plasma separated and aliquots were refrigerated at $-10°$ until analysis.

The area under the plasma concentration–time curve to the last sampling time $(AUC)_0^6$ was estimated by linear trapezoidal method and the area to infinity $(AUC)_0^\infty$ was calculated by adding onto AUC_0^6, the area obtained by dividing the last plasma concentration by the elimination rate constant. The elimination rate constant was determined by the linear regression analysis when the terminal plasma concentrations plotted on a logarithmic axis declined in a linear manner. Terminal half-lives were calculated from the log-linear part of the slope.

Cimetidine assay

Cimetidine was analysed by a modified HPLC method reported by Lorenzo and Drayer.[11] To a 150 µl of plasma aliquot to be assayed, 8 µl of $100\,\mu g\,ml^{-1}$ of SK&F 92374 (internal standard) and 15 µl of 6N NaOH were added. The mixture was extracted with 500 µl of 4 per cent isopropyl alcohol in ethyl

acetate by vortexing for 1 min. After centrifugation, the organic layer was transferred and evaporated to dryness at 80° under a stream of nitrogen. The residue was reconstituted in 50 μl spectroscopic grade methanol and 10 μl was injected onto the column. The column consisted of μ-Bondapack C_{18} cartridge (10 cm ×8 mm i.d.; Waters Associates). The mobile phase consisted of 10 per cent methanol in 5 mM K_2HPO_4 at pH 2·8. The flow-rate was set at 4 ml min^{-1}. The effluent was monitored at 225 nm with a detection scale of 0·01 or higher as needed. The retention times for internal standard and cimetidine were 2·6 and 5·0 min respectively. This method provided a low detection limit of 0·1 μg ml^{-1}.

Ranitidine assay

To a 250 μl of plasma aliquot to be assayed, 10 μl of 7 μg ml^{-1} of cimetidine (internal standard) and 25 μl of 6N NaOH is added. The mixture was extracted with 1·0 ml of 4 per cent isopropyl alcohol in ethyl acetate. The rest of the analytical method was similar to cimetidine with the exception that mobile phase consists of 15 per cent methanol in 5 mM K_2HPO_4 at pH 2·8 and the flow rate was 2 ml min^{-1}. The retention times for cimetidine and ranitidine were 5·4 and 7·0 min. This procedure provided a low detection limit of 0·25 μg ml^{-1}.

Statistical analysis

The difference between treatment were analysed by using Wilcoxon rank sum method.

RESULTS AND DISCUSSION

The mean profiles for cimetidine and ranitidine in rabbit plasma for the three treatments are shown in Figures 1 and 2, respectively. The mean plasma concentrations of cimetidine and ranitidine after oral concurrent administration of domperidone were significantly lower than the control up to 1·5 and 0·75 h, respectively. This effect was not observed with i.v. administration of domperidone. This may be due to the lower dose of i.v. domperidone (1 mg kg^{-1}) as compared to oral domperidone (2 mg kg^{-1}), even when intravenous dose was given 15 min prior to cimetidine and ranitidine administration. Lower intravenous dose was given in this study because previous absorption studies of domperidone indicated extensive first-pass effect in man.[12] Also, the mean plasma levels of cimetidine and ranitidine after i.v. domperidone administration were higher during the first 1·5 h and then lower as compared to current oral administration.

The computed pharmacokinetic parameters of cimetidine and ranitidine are presented in Table 1 and 2, respectively. There was a statistically significant domperidone effect on the AUC to 6 h and to infinity for both cimetidine and ranitidine. Overall, the mean decrease in AUC for oral and

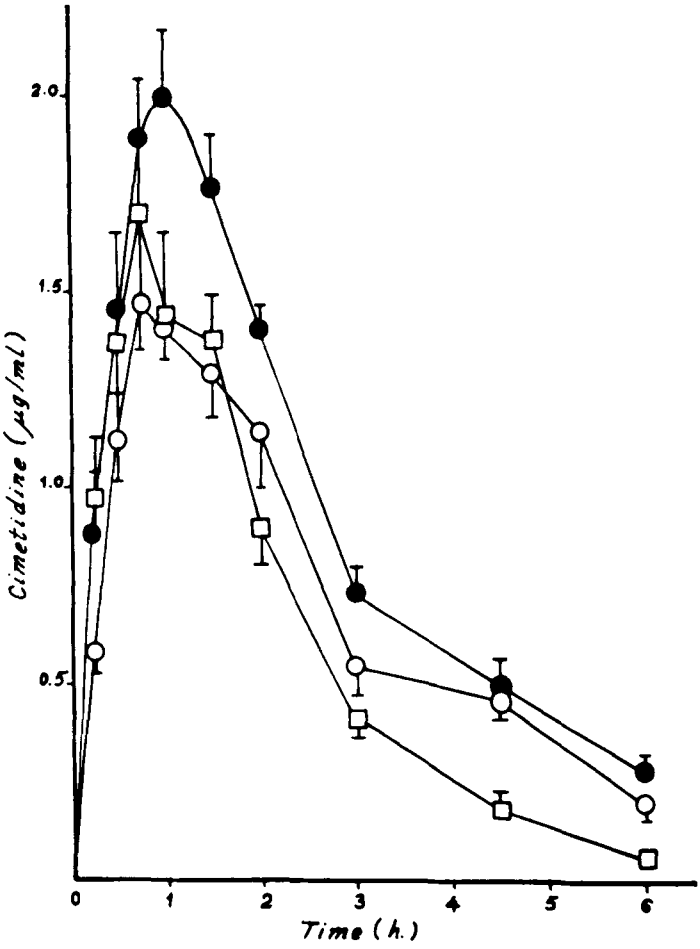

Figure 1. Plasma cimetidine concentration–time curves for 10 mg kg^{-1} oral dose of cimetidine alone (●) and in combination with oral (○) and intravenous (□) domperidone. Each point represents the mean ± S.E. for 6 rabbits in each treatment

i.v. domperidone administration was approximately 30 per cent for both drugs. Maximum plasma concentration (C_{max}), time taken to reach C_{max} (T_{max}), and $t_{1/2}$ of cimetidine and ranitidine were not significant between the treatments. The values of these variables varied widely among the rabbits. But in the same rabbit, the values for these variables were similar for all treatments. The half-lives of cimetidine and ranitidine were similar to those observed in previous studies[13,14] and were not significantly changed due to domperidone treatment.

Studies have shown alteration in drug absorption during concurrent administration of a drug which affects gastric emptying. Drug absorption

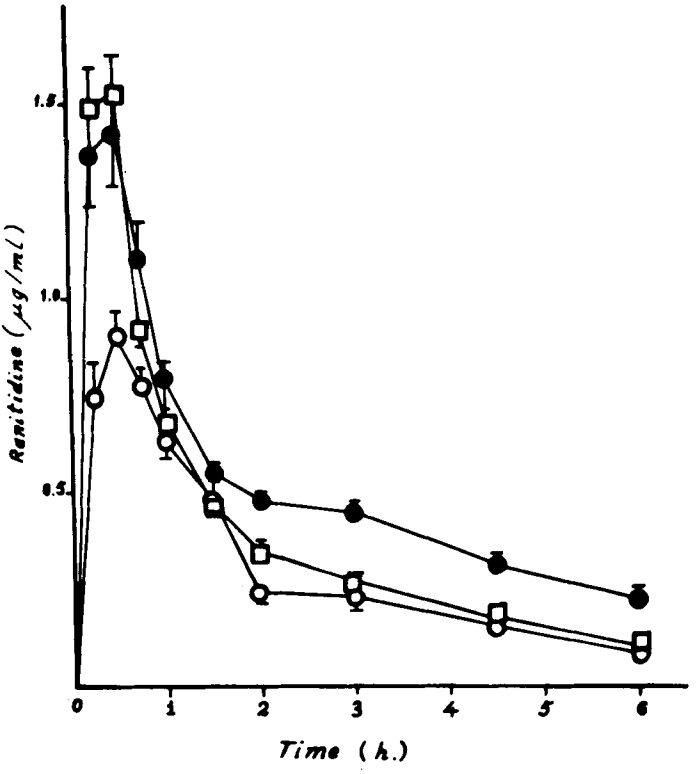

Figure 2. Plasma ranitidine concentration–time curves for 20 mg kg^{-1} oral dose of ranitidine (●) and in combination with oral (○) and intravenous (□) domperidone. Each point represents the mean ± S.E. for 6 rabbits in each treatment

Table 1. Computed parameters of cimetidine after oral administration of cimetidine alone and in combination with oral and intravenous domperidone in rabbit

Parameter	Domperidone		
	Without	Oral	Intravenous
AUC to 6h, μg.h ml^{-1}	5·4 ± 0·1*	3·9 ± 0·3†	3·8 ± 0·2†
AUC to infinity, μg.h ml^{-1}	6·0 ± 0·3	4·4 ± 0·4†	3·9 ± 0·2†
Time of maximum concentration, h	1·1 ± 0·1	1·1 ± 0·1	0·9 ± 0·1
Maximum concentration, μg ml^{-1}	2·6 ± 0·1	2·1 ± 0·1	2·3 ± 0·2
Terminal half-life, h	1·73 ± 2·2	1·6 ± 0·2	1·0 ± 0·1

* Mean ± S.E.
† Statistically significant ($p < 0·05$) to without domperidone.

Table 2. Computed parameters of ranitidine after oral administration of ranitidine alone and in comination with oral and intravenous domperidone in rabbits

Parameter	Domperidone		
	Without	Oral	Intravenous
AUC to 6h, μg.h ml^{-1}	3·1 ± 2·0*	1·9 ± 0·1†	2·4 ± 0·1†
AUC to infinity, μg.h ml^{-1}	4·6 ± 0·3	2·3 ± 0·1†	2·8 ± 0·1†
Time of maximum concentration, h	0·4 ± 0·1	0·7 ± 0·1	0·4 ± 0·1
Maximum concentration, μg ml^{-1}	1·5 ± 0·1	1·2 ± 0·1	1·7 ± 0·1
Terminal half-life, h	3·6 ± 0·4	2·8 ± 0·4	2·4 ± 0·1

* Mean ± S.E.
† Statistically significant ($p < 0·05$) to without domperidone.

from the small intestine is reported to occur earlier, if gastric emptying enhanced.[7] A decrease in GI transit time may result in incomplete absorption of a drug.[7] Oral domperidone has a tendency to reduce C_{max} in all the rabbits, although not significantly for cimetidine and ranitidine, indicating that these drugs are removed quickly from the first major absorption site.

The results obtained in this study are interpreted as a reduction in the amount of cimetidine and ranitidine absorbed into the systemic circulation on coadministration of domperidone. Similar reduction was observed when cimetidine is administered with metoclopramide.[9] Therefore, domperidone affected the extent but not the rate of cimetidine and ranitidine absorption in rabbits by enhancing gastric emptying. Since the effect of cimetidine on gastric acid secretion is closely correlated with its actual plasma concentration,[15] the dose of cimetidine and ranitidine may need to be increased to achieve proper therapeutic results.

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REFERENCES

1. D. P. D'Souza, A. Reyntjens and R. D. Thornes, *Curr. Therap. Res.*, **27**, 384 (1980).
2. O. Debontridden, *Lancet*, **1**, 802 (1980).
3. P. Sol, B. Pelet and J. P. Guignard, *Lancet*, **2**, 802 (1980).
4. M. Kataria, M. Traub and C. D. Marsden, *Lancet*, **2**, 1254 (1978).
5. R. A. Joss, A. Goldhirsh, K. W. Brunner and R. L. Galeazzi, *Lancet*, **1**, 1019 (1982).
6. J. B. Roussak and P. Carey, *Br. Med. J.*, **289**, 1579 (1984).
7. J. Nimmo, R. C. Heading, P. Tothill and L. F. Prescott, *Br. Med. J.*, **1**, 587 (1973).
8. S. Algeri, C. Cerletti, M. Curcio, P. L. Morselli, L. Bonollo, G. Bunira, M. Minazzi and G. Minoli, *J. Pharmacol.*, **35**, 293 (1976).

9. R. Gugler, M. Brand and A. Somogyi, *Eur. J. Clin. Pharmacol.*, **20**, 225 (1981).
10. J. Kanto, H. Allonen, H. Jalonen and R. Mantyla, *Br. J. Clin. Pharmacol.*, **11**, 629 (1981).
11. B. Lorenzo and D. E. Drayer, *J. Lab. Clin. Med.*, **97**, 545 (1981).
12. J. Heykants, R. Hendriks, W. Meuldermans, M. Michiels, H. Scheygrond and H. Reyntjens, *Eur. J. Drug Metab. Pharmacok.*, **6**, 61 (1981).
13. G. W. Mihaly, D. B. Jones, J. A. Anderson, R. A. Smallwood and W. J. Louis, *Br. J. Clin. Pharmacol.*, **17**, 109 (1984).
14. A. Varughese and C. S. C. Lee, *Drugs Exptl. Clin. Res.*, **9**, 837 (1983).
15. R. Gugler, G. Fuchs,, M. Diekmann and A. Somogyi, *Clin. Pharmacol. Ther.*, **29**, 744 (1981).