Effect of Cimetidine on the Pharmacokinetics and Pharmacodynamics of Chlorpheniramine and Diphenhydramine in Rabbits

Keith J. Simons,[1] Xueyu Chen,[2] Terry G. Fraser,[2] and F. Estelle R. Simons[3,4]

Received August 24, 1995; accepted November 17, 1995

Purpose. The effects of concomitant administration of the H_2-receptor antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-receptor antagonists chlorpheniramine and diphenhydramine were studied in rabbits.

Method. A single dose of chlorpheniramine 10 mg (Group A) or diphenhydramine 10 mg (Group B) was given intravenously on three different study days as follows: 2 weeks before cimetidine administration, after giving cimetidine 100 mg/kg intravenously every 12 hours for one week, and two weeks after discontinuing the cimetidine. Serum chlorpheniramine and diphenhydramine concentrations were measured by HPLC. Histamine H_1-blockade was assessed by measuring suppression of the histamine-induced wheals in the skin.

Results. The chlorpheniramine and diphenhydramine terminal elimination half-life values and area under the curve values were significantly increased, and the systemic clearance rates were significantly decreased, during concomitant administration of cimetidine. For each H_1-receptor antagonist, pharmacokinetic parameters were similar before cimetidine was co-administered and two weeks after cimetidine was discontinued. Wheal suppression produced by chlorpheniramine or diphenhydramine was increased and prolonged when cimetidine was administered concomitantly.

Conclusion. Any enhanced peripheral H_1-blockade observed could be attributed, at least in part, to a pharmacokinetic interaction.

KEY WORDS: chlorpheniramine; diphenhydramine; cimetidine; antihistamines; H_1- and H_2-receptor antagonist interactions.

INTRODUCTION

In the treatment of chronic urticaria, H_1-receptor antagonists do not always give optimal relief of itching, erythema, and whealing. In this situation, an H_2-receptor antagonist, usually cimetidine, is added to the treatment regimen, as concomitant administration of an H_1- and an H_2-receptor antagonist seems to enhance the efficacy of the H_1-antagonist (1,2). There is some evidence that a pharmacokinetic interaction between the H_1- and H_2-receptor antagonists may contribute to this increased effectiveness (3–5).

[1] Health Sciences Clinical Research Centre, Faculties of Pharmacy, Science, and Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

[2] Health Sciences Clinical Research Centre, Faculties of Pharmacy and Science, University of Manitoba, Winnipeg, Manitoba, Canada.

[3] Health Sciences Clinical Research Centre, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

[4] To whom correspondence should be addressed at: 820 Sherbrook Street, Winnipeg, Manitoba, Canada, R3A 1R9.

The older H_1-receptor antagonists chlorpheniramine and diphenhydramine are still widely used in the treatment of chronic urticaria. While their efficacy may be enhanced when they are concomitantly administered with cimetidine (6,7), their pharmacokinetic and pharmacodynamic interactions with cimetidine have not yet been adequately studied.

We hypothesized that cimetidine administered concomitantly with chlorpheniramine or diphenhydramine would inhibit their disposition, increase their concentrations in serum, and improve the peripheral H_1-blockade they produce. We tested this hypothesis in rabbits using suppression of the histamine-induced wheals as evidence of peripheral H_1-blockade.

METHODS

The research protocol was approved by the University of Manitoba Animal Care Committee and the studies were conducted according to the guidelines published by the Canadian Council on Animal Care.

Five New Zealand white rabbits (mean weight 4.3 ± 0.3 kg) were used for the chlorpheniramine study (Group A) and five rabbits (mean weight 3.9 ± 0.2 kg) were used for the diphenhydramine study (Group B). Each rabbit was kept individually in a metal cage with a wire floor support to reduce coprophagy. Food and water were supplied ad libitum throughout each study.

In Group A, chlorpheniramine (Schering, Pointe-Claire, Quebec, Canada H9R 1B4) and in Group B, diphenhydramine (Warner Wellcome Inc., Scarborough, Ontario, Canada M1L 2N3) were administered using the commercially available formulations for intravenous use. Each rabbit in Group A received a single intravenous 10 mg dose of chlorpheniramine. Two weeks later, cimetidine 100 mg/kg (Tagamet injection, 150 mg/mL, SmithKline Beecham Pharma Inc., Oakville, Ontario, Canada L6H 5V2) was given intravenously every 12 hours for seven days. On the seventh day, immediately after the morning cimetidine dose, chlorpheniramine 10 mg intravenously was administered again and cimetidine was discontinued. Two weeks later, a third intravenous 10 mg dose of chlorpheniramine was given.

In Group B, the study was performed in an identical manner, except that on the three study days when an H_1-receptor antagonist was given, diphenhydramine 10 mg was administered intravenously instead of chlorpheniramine.

In both Group A and Group B, before, and at 0.1, 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours after chlorpheniramine or diphenhydramine administration intravenously in an ear vein, two mL blood samples were collected from a vein in the opposite ear using an in-dwelling catheter with a "heparin lock". When cimetidine was coadministered, additional blood samples were taken 10 and/or 12 hours after chlorpheniramine or diphenhydramine administration. Before each blood sample was obtained, 1 mL of blood and heparinized saline were withdrawn from the catheter and discarded; afterwards, the catheter was rinsed with 1–2 mL saline followed by 0.4 mL Hep-Lock solution containing 100 I.U. heparin/mL. All blood samples were collected in 16 × 100 mm glass test tubes without anti-coagulant. The serum was separated by placing Sure-Sep II separators (Organon Teknika Corp., Durham, NC, U.S.A. 27704) on top

of the samples in the test tubes and centrifuging for 15 minutes at 2000 rpm. Serum samples were stored at −20°C until analyzed.

At the beginning of each pharmacokinetic study, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase were measured in the Health Sciences Clinical Chemistry laboratory.

The day before study, each rabbit's back was shaved. Immediately before the study, a depilatory was used to remove any remaining hair. Each time a blood sample was taken, the efficacy of chlorpheniramine or diphenhydramine was assessed using an intradermal injection of 0.05 mL of histamine phosphate, 1.0 mg/mL. Skin tests were performed before chlorpheniramine or diphenhydramine administration, and afterwards at the same times at which the blood samples were obtained. A different site on the back was used for each test. Before the first test, 0.1 mL of Evans blue, 100 mg/mL, was injected intravenously to facilitate identification of the wheal border. The cutaneous blue spots were traced 10 minutes after each histamine injection and transferred to transparent paper using pen. Wheal areas were measured with an IBM-XT-compatible computer fitted with a digitizer and stereometric measurement software (Sigma Scan Version 3.10, Jandel Scientific, San Raphael, CA 94901).

Serum chlorpheniramine and diphenhydramine concentrations were determined by HPLC methods developed previously in our laboratory (8,9).

Data Analysis

Pharmacokinetic parameters were calculated using standard equations and the PKCALC interactive computer program on an IBM-XT-compatible computer (10,11). The arithmetic mean ± standard deviation was used in the analysis of all parameters except for the serum elimination half life, which was analyzed using the harmonic mean and jackknife standard deviation. Serum chlorpheniramine and diphenhydramine concentrations versus time data after intravenous bolus injection could be best described by a two-compartment model.

Two-way blocked ANOVA using subject and sample time for within study-day analysis, or subject and treatment for between day analysis, as the criteria of classification, and the Tukey and Bonferroni multiple-range tests were used for all comparisons of pharmacokinetic and peripheral H_1-antagonist blockade parameters.

It was not possible to calculate any pharmacodynamic parameters using the E_{max} model as there were too few samples and a considerable loop of hysteresis was noted in data from all animals (12).

Differences were considered significant at $p < 0.05$ (13).

RESULTS

Assessment of Hepatic Function

Mean serum AST, ALT, LDH, and alkaline phosphatase concentrations increased in each individual animal when cimetidine was administered and decreased to pre-cimetidine values when cimetidine was discontinued. The mean differences were not statistically significant due to the wide inter-animal variability in enzyme levels before cimetidine administration and the wide inter-animal variability in increase in enzyme levels after cimetidine administration.

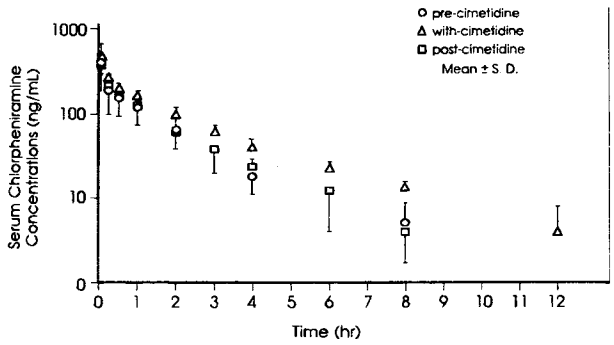

Fig. 1. Mean serum chlorpheniramine concentration versus time plots after an intravenous injection of 10 mg chlorpheniramine before, during, and after the coadministration of cimetidine.

Group A

Pharmacokinetics of Chlorpheniramine

After an intravenous injection of 10 mg chlorpheniramine, the serum chlorpheniramine concentration versus time plot (Figure 1) was best described by a biexponential equation. Pharmacokinetic parameters are shown in Table I. When chlorpheniramine was administered concomitantly with cimetidine, the terminal elimination half-life value and the area under the curve increased significantly and the clearance rate decreased significantly.

Pharmacodynamics of Chlorpheniramine

Compared to pre-dose values, histamine induced wheals were significantly suppressed for 0.5 hours after chlorpheniramine alone; when cimetidine was administered concurrently, significant suppression of wheals lasted for 3 hours. From 0.5 to 8h, wheal suppression following the co-administration of cimetidine with chlorpheniramine was significantly greater than wheal suppression following chlorpheniramine alone (Figure 2). No pharmacodynamic parameters could be calculated.

Table I.

Chlorpheniramine Pharmacokinetics	Pre-Cimetidine	With Cimetidine	Post-Cimetidine
t1/2 (h)	1.6 ± 0.3	2.1 ± 0.4*	1.4 ± 0.2
AUC (ng•h/mL)	452 ± 55	597 ± 56*	398 ± 71
Cl (mL/min)	361 ± 50	270 ± 24*	421 ± 80
Vd_{ss} (L)	44.5 ± 9.3	45.6 ± 9.8	46.0 ± 4.5
MRT (h)	2.1 ± 0.5	2.8 ± 0.4	1.9 ± 0.3
WA (max % suppr.)	39.6 ± 9.8	52.4 ± 11.2	not studied

* $p \leq 0.05$
t1/2—terminal elimination half-life
AUC—area under the curve
Cl—clearance
Vd_{ss}—volume of distribution at steady-state
MRT—mean residence time
WA—wheal area

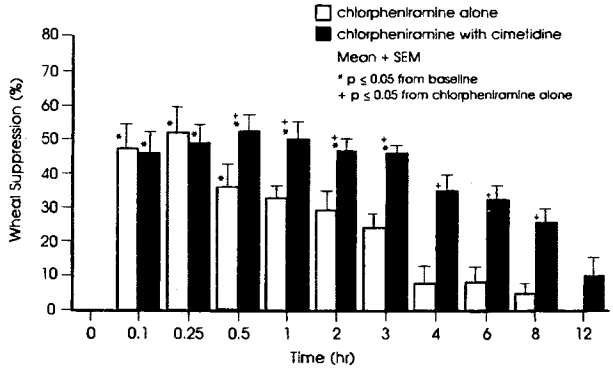

Fig. 2. Mean percent suppression of histamine-induced wheals by chlorpheniramine 10 mg intravenously alone and during coadministration of cimetidine.

Table II.

Diphenhydramine pharmacokinetics	Pre-Cimetidine	With Cimetidine	Post-Cimetidine
t1/2 (h)	1.3 ± 0.2	1.9 ± 0.4*	1.3 ± 0.4
AUC (ng•h/mL)	363 ± 173	618 ± 59*	320 ± 58
Cl (mL/min)	500 ± 179	259 ± 24*	506 ± 88
Vd_{ss} (L)	53.2 ± 27.4	42.3 ± 15.4	55.2 ± 13.5
MRT (h)	1.7 ± 0.4	2.6 ± 1.2	1.9 ± 0.4
WA (max % suppr.)	39.6 ± 9.8	64.5 ± 23.3	not studied

* $p < 0.05$.
t1/2—terminal elimination half-life.
AUC—area under the curve.
Cl—clearance.
Vd_{ss}—volume of distribution at steady-state.
MRT—mean residence time.
WA—wheal area.

Group B

Pharmacokinetics of Diphenhydramine

After an intravenous injection of 10 mg diphenhydramine, the serum diphenhydramine concentration versus time plot (Figure 3) was best described by a biexponential equation. Pharmacokinetic parameters are shown in Table II. When diphenhydramine was administered concomitantly with cimetidine, the terminal elimination half-life value and the area under the curve increased significantly and the clearance rate decreased significantly.

Pharmacodynamics of Diphenhydramine

Compared to pre-dose values, histamine induced wheals were significantly suppressed for 0.25 hours after diphenhydramine alone; when cimetidine was administered concurrently with diphenhydramine, significant suppression of wheals lasted for 3 hours. At 0.1 hour, wheal suppression following the coadministration of cimetidine was significantly greater than wheal suppression following diphenhydramine alone (Figure 4). No pharmacodynamic parameters could be calculated.

DISCUSSION

Chlorpheniramine and diphenhydramine doses of 10 mg were selected for this study because 10 mg H_1-receptor antagonist doses have been used previously in this model of H_1-H_2-receptor antagonist interaction (4). No attempt was made to select maximally effective H_1-antagonist doses; submaximal doses were desirable in order to allow for the possibility of enhanced effect during co-administration of the H_1- and H_2-antagonists.

Cimetidine potentially increases the serum concentrations, tissue concentrations, and duration of action of many concomitantly administered medications metabolized in the liver (14–16). It may affect the hepatic elimination of these medications in two ways: by binding to the heme portion of the cytochrome P_{450} system of mixed-function oxidases and resulting in decreased metabolism of medications that are poorly-extracted in the liver, or by reducing hepatic blood flow and decreasing clearance of medications that are highly extracted in the liver. In the present study, the precise mechanism by which it inhibited the elimination of chlorpheniramine and diphenhydramine, as evidenced by elevation of the serum chlorpheniramine and diphenhydramine concentrations, is not known, but likely involved competitive inhibition of oxidative demethylation, since chlorpheniramine and diphenhydramine have low to medium extraction ratios (17,18), and both drugs are metabolised by oxidative demethylation (19,20).

In addition to affecting metabolism, cimetidine may interact with other medications by influencing their absorption, for example, by inhibiting gastric acid secretion due to its H_2-

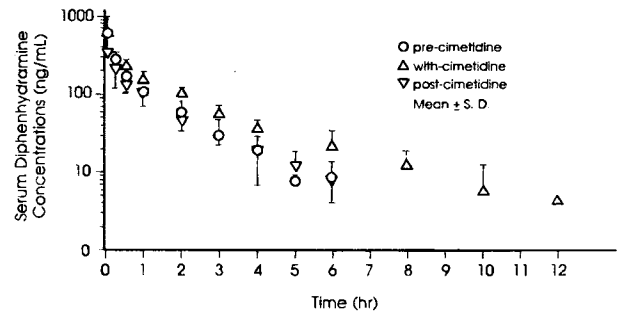

Fig. 3. Mean serum diphenhydramine concentration versus time plots after an intravenous injection of 10 mg diphenhydramine before, during, and after the coadministration of cimetidine.

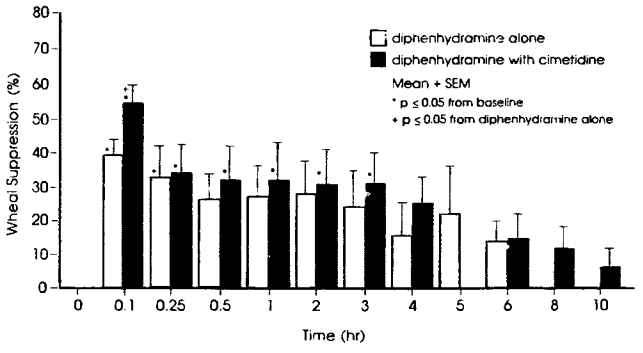

Fig. 4. Mean percent suppression of histamine-induced wheals by diphenhydramine 10 mg intravenously alone and during coadministration of cimetidine.

receptor blocking activity, and increasing the pH of the contents of the stomach and the proximal duodenum. This can lead to differences in the rate and extent of absorption of medications that require low pH for disintegration or dissolution. In this study, it is highly unlikely that cimetidine affected serum H_1-receptor antagonist absorption, as all medications were administered intravenously.

Cimetidine may also interact with other medications by competing for renal tubular secretion, but as chlorpheniramine and diphenhydramine are not eliminated to any great extent as unchanged drug via the renal route (19,20), it is unlikely that this mechanism contributed significantly to the elevated serum chlorpheniramine and diphenhydramine concentrations found in the present study.

The peripheral H_1-blockade effect of both chlorpheniramine and diphenhydramine was enhanced when they were administered concurrently with cimetidine. The pharmacodynamic interaction was greater for chlorpheniramine/cimetidine than for diphenhydramine/cimetidine. In previous studies of H_1-H_2-receptor antagonist pharmacokinetic and pharmacodynamic interactions in rabbits and in humans, the H_1-receptor antagonists administered have been hydroxyzine or cetirizine (3–5). An important limitation of these studies is that these two H_1-receptor antagonists suppress the histamine-induced wheal almost completely when administered alone, leaving little room for demonstration of the additive suppressive effect of a concomitantly administered H_2-receptor antagonist. In this study, we avoided this problem by administering chlorpheniramine and diphenhydramine, H_1-receptor antagonists with more modest peripheral H_1-blockade effects.

While the increased effectiveness of H_1-antagonists when co-administered with the H_2-antagonist is attributed in part to the pharmacokinetic interaction between the H_1- and H_2-antagonists, a synergistic effect of H_1- and H_2-receptor antagonists at the receptor level cannot be ruled out. In the present study, cimetidine alone had a negligible suppressive effect on the histamine-induced wheals, as observed before the H_1-antagonist dose on study day 2, compared to the wheals observed before the H_1-antagonist dose on study day 1. In other studies, H_2-receptor antagonists, like H_1-receptor antagonists, have been shown to produce direct blockade of histamine-induced increased permeability of the post-capillary venules and prevent the passage of plasma protein into the extravascular space (21).

Potential drug interactions with H_1-receptor antagonists eliminated primarily by the hepatic microsomal cytochrome P_{450} 3A4 system are now identified initially by screening *in vitro* liver microsome preparations (22). While this method is extremely useful for studying pharmacokinetic interactions, it is less useful for investigation of pharmacodynamic interactions. Investigation of H_1-receptor antagonists and H_2-receptor antagonists in an animal model permitted study of their combined synergistic effects on peripheral H_1-receptor blockade in the skin, in addition to study of their pharmacokinetic interaction.

REFERENCES

1. F. E. R. Simons and K. J. Simons. The pharmacology and use of H_1-receptor antagonist drugs. *N. Engl. J. Med.* **330**:1663–1670 (1994).
2. M. W. Greaves. Chronic urticaria. *N. Engl. J. Med.* **332**:1767–1772 (1995).
3. O. P. Salo, K. Kauppinen, and P. T. Männistö. Cimetidine increases the plasma concentration of hydroxyzine. *Acta. Derm. Venereol.* (Stockh). **66**:349–350 (1986).
4. X. Chen, F. E. R. Simons, and K. J. Simons. Effect of the H_2-receptor antagonist cimetidine, on the pharmacokinetics and pharmacodynamics of the H_1-receptor antagonists hydroxyzine and cetirizine in rabbits. *Pharmaceut. Res.* **11**:295–300 (1994).
5. F. E. R. Simons, G. L. Sussman, and K. J. Simons. Effect of the H_2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J. Allergy Clin. Immunol.* **95**:685–693 (1995).
6. S. S. Bleehen, S. E. Thomas, M. W. Greaves, J. Newton, C. T. C. Kennedy, F. Hindley, R. Marks, M. Hazell, N. R. Rowell, G. M. Fairiss, P. H. Cartwright, H. P. Glenny, and K. Howland. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br. J. Dermatol.* **117**:81–88 (1987).
7. L. E. Mansfield, J. A. Smith, and H. S. Nelson. Greater inhibition of dermographia with a combination of H_1 and H_2 antagonists. *Ann. Allergy* **50**:264–265 (1983).
8. F. E. R. Simons, G. H. Luciuk, and K. J. Simons. Pharmacokinetics and efficacy of chlorpheniramine in children. *J. Allergy Clin. Immunol.* **69**:376–381 (1982).
9. K. J. Simons, W. T. A. Watson, T. J. Martin, X. Y. Chen, and F. E. R. Simons. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. *J. Clin. Pharmacol.* **30**:665–671 (1990).
10. M. Gibaldi and D. Perrier. Pharmacokinetics, Marcel Dekker, Inc., New York, 1982.
11. R. C. Shumaker. PKCALC: A BASIC interactive computer program for statistical and pharmacokinetic analysis of data. *Drug Metab. Rev.* **17**:331–348 (1986).
12. T. L. Schwinghammer and P. D. Kroboth. Basic concepts in pharmacodynamic modeling. *J. Clin. Pharmacol.* **28**:388–394 (1988).
13. J. Neter, W. Wasserman, and M. H. Kutner. Applied Linear Statistical Models. Regression, Analysis of Variance, and Experimental Designs, Irwin, Boston, MA, 1990.
14. A. Somogyi and M. Muirhead. Pharmacokinetic interactions of cimetidine 1987. *Clin. Pharmacokinet.* **12**:321–366 (1987).
15. S. R. Smith and M. J. Kendall. Ranitidine versus cimetidine. A comparison of their potential to cause clinically important drug interactions. *Clin. Pharmacokinet.* **15**:44–56 (1988).
16. M. Feldman and M. E. Burton. Histamine$_2$-receptor antagonists. Standard therapy for acid-peptic diseases. *N. Engl. J. Med.* **323**:1672–1680 (1990).
17. S. M. Huang, N. K. Athanikar, K. Sridhar, Y. C. Huang, and W. L. Chiou. Pharmacokinetics of chlorpheniramine after intravenous and oral administration in normal adults. *Eur. J. Clin. Pharmacol.* **22**:359–365 (1982).
18. C. G. Meredith, C. D. Christian Jr, R. F. Johnson, S. V. Madhavan, and S. Schenker. Diphenhydramine disposition in chronic liver disease. *Clin. Pharmacol. Ther.* **35**:474–479 (1984).
19. K. J. Simons, F. E. R. Simons, G. H. Luciuk, and E. M. Frith. Urinary excretion of chlorpheniramine and its metabolites in children. *J. Pharm. Sci.* **73**:595–599 (1984).
20. A. J. Glazko, W. A. Dill, R. M. Young, T. C. Smith, and R. I. Ogilvie. Metabolic disposition of diphenhydramine. *Clin. Pharmacol. Ther.* **16**:1066–1076 (1974).
21. R. Marks and M. W. Greaves. Vascular reactions to histamine and compound 48/80 in human skin: suppression by a histamine H_2-receptor blocking agent. *Br. J. Clin. Pharmacol.* **4**:367–369 (1977).
22. L. L. von Moltke, D. J. Greenblatt, S. X. Duan, J. S. Harmatz, and R. I. Shader. In vitro prediction of the terfenadine-ketoconazole pharmacokinetic interaction. *J. Clin. Pharmacol.* **34**:1222–1227 (1994).