Effect of the H_2-Receptor Antagonist Cimetidine, on the Pharmacokinetics and Pharmacodynamics of the H_1-Receptor Antagonists Hydroxyzine and Cetirizine in Rabbits

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The effects of coadministration of the H_2-receptor antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-receptor antagonists hydroxyzine and cetirizine were studied in rabbits. A single dose of hydroxyzine, 10 mg (Experiment A), or cetirizine, 10 mg (Experiment B), was given intravenously on three occasions: 2 weeks before cimetidine administration, after cimetidine, 100 mg/kg, had been given every 12 hr for 1 week, and 2 weeks after the cimetidine was discontinued. Serum concentrations of hydroxyzine and cetirizine, the active metabolite of hydroxyzine arising *in vivo* (Experiment A), or cetirizine (Experiment B) were measured by HPLC. The pharmacologic effects of hydroxyzine and cetirizine were monitored by measuring the suppression of histamine-induced wheals, using an IBM-PC and digitizer. The hydroxyzine and cetrizine half-life and $AUC_{0\rightarrow\infty}$ values were significantly increased and the systemic clearance rates were significantly decreased in the presence of cimetidine. Similar results were obtained when cetirizine was administered de novo. Wheal suppression produced by hydroxyzine or cetirizine was increased and prolonged in the presence of cimetidine. The synergism observed between hydroxyzine or cetirizine and cimetidine in suppression of the histamine-induced cutaneous response may be due to a pharmacokinetic interaction.

KEY WORDS: hydroxyzine; cetirizine; cimetidine; H_1- and H_2-receptor antagonist interaction.

INTRODUCTION

Histamine H_1-receptor antagonists inhibit the histamine-induced cutaneous wheal and flare response to varying degrees (1–6). The H_1-antagonists hydroxyzine and cetirizine have a potent effect in suppressing this response (1–6). *In vivo,* about 60% of a dose of hydroxyzine is converted to the active metabolite, cetirizine, which has been introduced as a new, relatively nonsedating H_1-antagonist for de novo administration (6).

Histamine H_2-antagonists have a weak effect on suppression of the histamine-induced wheal and flare response (7). Concomitant administration of an H_1- and an H_2-antagonist is more effective than administration of either antagonist alone (7–9). It is possible that a kinetic interaction between an H_1- and an H_2-antagonist (10,11) is responsible for the increased effectiveness. One report indicated that serum hydroxyzine concentrations were increased in the presence of cimetidine (12).

We hypothesized that (a) the H_2-antagonist cimetidine would inhibit the disposition of the H_1-antagonist hydroxyzine and increase the serum hydroxyzine concentrations; (b) cimetidine would also inhibit the disposition of cetirizine, whether formed from hydroxyzine *in vivo* or administered de novo; (c) the enhanced effect of hydroxyzine and cetirizine on suppression of the histamine-induced wheal by the presence of cimetidine might be due to increased hydroxyzine and cetirizine serum and tissue H_1-antagonists concentrations; and (d) these effects would be reversible. We tested the effect of the coadministration of cimetidine on the disposition of hydroxyzine and cetirizine in rabbits, using suppression of the histamine-induced wheals as evidence of H_1- and H_2-antagonist activity.

METHODS

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

Five New Zealand white rabbits, mean weight 3.9 ± 0.5 kg, were used for the hydroxyzine study (Experiment A) and five rabbits, mean weight 3.9 ± 0.5 kg, were used for the cetirizine study (Experiment 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.

Hydroxyzine and cetirizine solutions for intravenous administration were freshly prepared by dissolving hydroxyzine HCl or cetirizine HCl, pure substances (Pfizer Canada Inc., Kirkland, Quebec, Canada), in water, 10 mg/mL, and sterilized by filtering through a 0.22-μm Millipore filter. Each rabbit in Experiment A received a single intravenous 10 mg dose of hydroxyzine. Two weeks later, cimetidine 100 mg/kg (Tagamet injection, 150 mg/mL; Smith Kline & French, Oakville, Ontario, Canada), was given intravenously every 12 hr for 7 days. On the seventh day, immediately after the morning cimetidine dose, an intravenous 10-mg dose of hydroxyzine was administered again, and cimetidine was discontinued. Two weeks later, another intravenous 10-mg dose of hydroxyzine was given. In Experiment B, the study was performed in rabbits using cetirizine, 10 mg iv, instead of hydroxyzine.

During Experiments A and B, 2-mL blood samples were collected from the ear vein at −0.1, 0.1, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hr after hydroxyzine or cetirizine administration, via a butterfly infusion set (Sherwood Medical, St. Louis, MO) with a "heparin lock." When cimetidine was coadministered, an additional blood sample

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was taken 24 hr after hydroxyzine or cetirizine administration. All blood samples were collected in 16 × 100-mm glass test tubes without anticoagulant. The serum was separated by placing Sure-Sep II Separators (Organon Teknika Corp., Durham, NC) on top of the samples in the test tubes and centrifuging for 15 min at 2000 rpm. Serum samples were stored at −20°C until analyzed.

At the beginning of each study, an extra 5-mL blood sample was collected for quantitation of aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and alkaline phosphatase at the Health Sciences Clinical Chemistry laboratory.

The day before each study, the rabbit's back was shaved. On the morning of the study, the back was treated with a depilatory to remove all hair. Each time a blood sample was taken, the efficacy of hydroxyzine or cetirizine was assessed using an intradermal injection of 0.05 mL of histamine phosphate, 1.0 mg/mL. 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 min after each histamine injection and transferred to transparent paper using a felt-tipped 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, Sausalito, CA) (2,4,5).

Serum hydroxyzine and cetirizine concentrations, the latter arising *in vivo* as the active metabolite of hydroxyzine (Experiment A), and serum cetirizine concentrations (Experiment B) were determined by HPLC methods developed previously in our laboratory (2,4). In the hydroxyzine assay, the flow rate was set at 0.8 mL/min, and the retention times for hydroxyzine and the internal standard were 5.0 and 11.0 min, respectively. In the cetirizine assay, at a flow rate of 1.2 mL/min, the retention times for cetirizine and the internal standard were 6.0 and 7.5 min, respectively. The lower limits of sensitivity of the HPLC assays for hydroxyzine and cetirizine were 1.0 and 2.0 ng/mL, with day-to-day coefficients of variation of 6.0 ± 3.4 and 7.1 ± 4.9%, respectively, over 12 months.

Data Analysis

Pharmacokinetic parameters were calculated using the equations reported previously (2,4,13) and the PKCALC interactive computer program (14) on an IBM-XT-compatible computer. The serum hydroxyzine and cetirizine concentration versus time data after intravenous bolus injections of 10 mg hydroxyzine (Experiment A) or 10 mg cetirizine (Experiment B), respectively, could best be described by a two-compartment model. In Experiment A, the serum cetirizine concentration versus time data after intravenous bolus injections of 10 mg hydroxyzine could best be described by a two-compartment model with a first-order formation process (13). In Experiment A, the ratio (R) of cetirizine $AUC_{0\to\infty}$ to hydroxyzine $AUC_{0\to\infty}$ was determined following calculation of the individual $AUC_{0\to\infty}$ values by the trapezoid rule from time 0 to time t of the last sample and extrapolation to infinity.

The histamine-induced wheal areas were analyzed as percentage reduction of predose values, using Eq. (1):

$$E = \frac{A_0 - A_t}{A_0} \times 100\% \quad (1)$$

where A_0 is the wheal area before drug administration. A_t is the wheal area at time t after hydroxyzine and/or cetirizine administration.

The efficacy–concentration relationship was fitted into the E_{max} model (15,16), Eq. (2), on a mainframe computer at the University of Manitoba Computer Service using BMDP.

$$E = \frac{E_{max} \cdot C}{EC_{50} + C} \quad (2)$$

where E_{max} is the maximum effect that can be attributed to the drug, EC_{50} is the concentration that produced 50% of the maximum effect, and C is a modified concentration (15) for the hydroxyzine study (Experiment A), calculated using Eq. (3) (6).

$$C = C_{hydroxyzine} + 1/4\, C_{cetirizine} \quad (3)$$

where $C_{hydroxyzine}$ is the concentration of hydroxyzine at time t after hydroxyzine administration, and $C_{cetirizine}$ is the concentration of cetirizine at time t after hydroxyzine administration.

The two-way ANOVA using subject and sample time or subject and treatment as the criteria of classification and the Tukey and Bonferroni multiple-range tests were used for all comparisons. Differences were considered significant at $P < 0.05$ (17).

RESULTS

Biochemical Tests for Assessment of Hepatic Function

Mean serum AST, ALT, LDH, and alkaline phosphatase concentrations increased when cimetidine was administered and decreased to precimetidine values when cimetidine was discontinued, but the differences were not statistically significant.

Experiment A

Pharmacokinetics of Hydroxyzine

After an intravenous injection of 10 mg hydroxyzine, the resulting serum hydroxyzine concentration versus time plot (Fig. 1) was best described by a biexponential equation. The coefficients of determination ranged from 0.95 to 0.99.

The serum elimination half-life value ($t_{1/2}$) of hydroxyzine was 1.3 ± 0.4 hr before cimetidine treatment, increased significantly, to 4.3 ± 1.4 hr, during cimetidine treatment, and decreased to 1.3 ± 0.3 hr 2 weeks after cimetidine was discontinued. When cimetidine was coadministered with hydroxyzine, the systemic clearance of hydroxyzine, 20.2 ± 5.8 mL/min/kg, was significantly reduced compared to precimetidine and postcimetidine values of 52.3 ± 23.7 and 45.1 ± 11.4 mL/min/kg, respectively. When cimetidine was given concurrently with hydroxyzine, the hydroxyzine area under the curve ($AUC_{0\to\infty}$), 2133 ± 591 ng · hr/mL, was significantly increased compared to the precimetidine and postcimetidine values of 874 ± 317 and 905 ± 277 ng · hr/

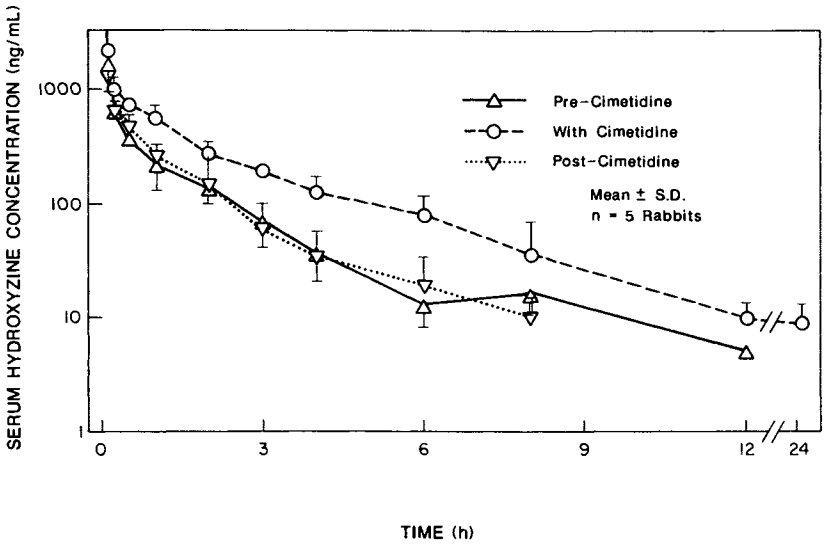

Fig. 1. Mean serum hydroxyzine concentration versus time plots after an intravenous injection of 10 mg hydroxyzine before, during, and after the coadministration of cimetidine.

mL, respectively. The apparent volumes of distribution of hydroxyzine did not differ significantly during the study, with values of 6.7 ± 2.6, 7.5 ± 3.8, and 4.9 ± 0.6 L/kg being found precimetidine, with cimetidine, and postcimetidine, respectively.

Pharmacokinetics of Cetirizine Arising in Vivo *as Hydroxyzine Metabolite*

After the intravenous injection of 10 mg hydroxyzine the serum cetirizine concentration versus time plots (Fig. 2) were best described by a triexponential equation. The $t_{1/2}$ of cetirizine was 1.7 ± 0.4 hr before cimetidine treatment, 3.7 ± 1.8 hr during cimetidine treatment, and 1.7 ± 0.4 hr 2 weeks after cimetidine was discontinued. Since cetirizine was appearing as a metabolite of hydroxyzine, these $t_{1/2}$ values probably reflect the $t_{1/2}$ of hydroxyzine (13). When cimetidine was coadministered with hydroxyzine, the cetirizine $AUC_{0\to\infty}$, 2602 ± 822 ng · hr/mL, was significantly increased compared to the precimetidine and postcimetidine values of 724 ± 147 and 538 ± 117 ng · hr/mL, respectively. Also, the maximum cetirizine concentration (C_{max}), 648 ± 275 ng · hr/mL, was significantly increased from the pre- and postcimetidine values of 244 ± 101 and 185 ± 69 ng/mL, respectively. The time of maximum cetirizine concentration (T_{max}), 1.3 ± 1.2 hr precimetidine, 1.0 ± 0 hr with cimetidine, and 0.9 ± 0.3 hr postcimetidine, did not change significantly. The ratio (R) of cetirizine $AUC_{0\to\infty}$ to hydroxyzine $AUC_{0\to\infty}$, 1.3 ± 0.5, was increased, compared to the precimetidine and postcimetidine values of 0.9 ± 0.4 and 0.7 ± 0.3, respectively, but this increase was not statistically significant.

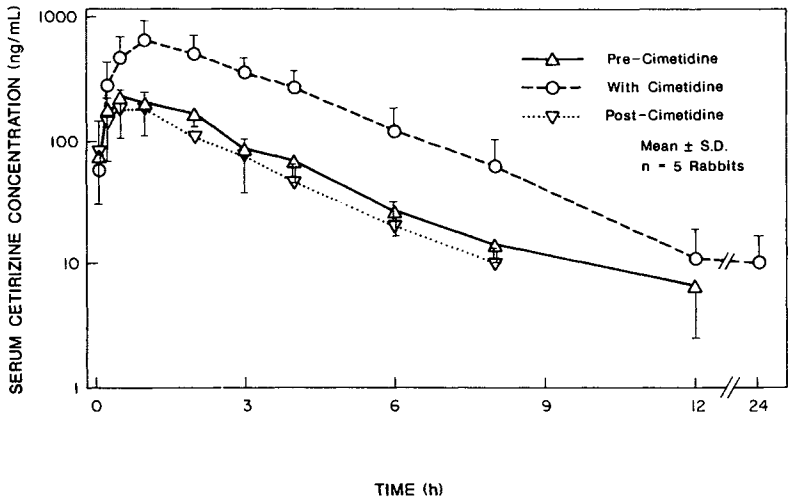

Fig. 2. Mean serum cetirizine concentration versus time plots after an intravenous injection of 10 mg hydroxyzine before, during, and after the coadministration of cimetidine.

Experiment B

Pharmacokinetics of Cetirizine Given de Novo

After an intravenous injection of 10 mg cetirizine, the resulting serum cetirizine concentration versus time plot (Fig. 3) was best described by a biexponential equation. The coefficients of determination ranged from 0.98 to 1.00. The $t_{1/2}$ of cetirizine was 1.2 ± 0.2 hr before cimetidine treatment, increased significantly to 4.1 ± 1.9 hr, during cimetidine treatment, and decreased to 1.4 ± 0.3 hr 2 weeks after cimetidine was discontinued. When cimetidine was coadministered with cetirizine, the systemic clearance of cetirizine, 5.2 ± 0.2 mL/min/kg, was significantly reduced compared to the precimetidine and postcimetidine values of 7.0 ± 0.7 and 7.4 ± 1.3 mL/min/kg, respectively. When cimetidine was given concurrently with cetirizine, the cetirizine $AUC_{0\to\infty}$, 8259 ± 1506 ng · hr/mL, was significantly increased compared to the precimetidine and postcimetidine values of 6192 ± 887 and 5906 ± 1005 ng · hr/mL, respectively. The apparent volumes of distribution of cetirizine did not differ significantly during the study, with values of 0.7 ± 0.1, 1.9 ± 1.0, and 0.9 ± 0.1 L/kg being found precimetidine, with cimetidine, and postcimetidine, respectively.

Experiment A

Pharmacodynamics of Hydroxyzine

After a single dose of 10 mg hydroxyzine, histamine-induced wheals were significantly suppressed for up to 12 hr compared to predose values (Fig. 4). The maximum suppression, compared to all other wheal areas measured during the study, occurred from 0.25 to 6.0 hr, when the wheals were 69.7 to 89.7% suppressed. The calculated E_{max} was 92.0%, and a concentration of 8.9 ng/mL was needed to achieve half of the maximum effect (EC_{50}). When cimetidine was given at the same time as hydroxyzine, significant suppression of wheals persisted for 24 hr compared to the predose values. Maximum suppression, compared to all other wheal areas measured during the study, occurred from 0.25 to 8.0 hr, when wheals were 77.4 to 98.8% suppressed. The E_{max} calculated was 99.2% and the EC_{50} was 9.3 ng/mL, not significantly different from the precimetidine values. Two weeks after the discontinuation of cimetidine, the suppressive effects of hydroxyzine on the histamine-induced wheals returned to the precimetidine values. The calculated E_{max} was 96.1% and the EC_{50} was 9.2 ng/mL.

Experiment B

Pharmacodynamics of Cetirizine Given de Novo

After a single dose of 10 mg cetirizine, histamine-induced wheals were significantly suppressed for up to 12 hr compared to predose values (Fig. 5). The maximum suppression, compared to all other wheal areas measured during the study, occurred from 0.08 to 8.0 hr, when the wheals were 75.5 to 98.4% suppressed. When cimetidine was given at the same time as cetirizine, significant suppression of wheals persisted for 24 hr compared to the predose values. Maximum suppression, compared to all other wheal areas measured during the study, occurred from 0.08 to 12.0 hr, when wheals were 75.5 to 98.4% suppressed. Two weeks after the discontinuation of cimetidine, wheals were significantly suppressed up to 12 hr. Maximum suppression, compared to all other wheal areas measured during the study, occurred from 0.08 to 8 hr, when wheals were 77.6 to 98.1% suppressed. It was not possible to fit the data from Experiment B by Eq. (2), so values of E_{max} and EC_{50} could not be calculated.

DISCUSSION

In the rabbit model, we have confirmed our hypotheses that (a) coadministration of cimetidine and hydroxyzine would significantly inhibit the disposition of hydroxyzine; (b) the disposition of cetirizine, whether formed from hydroxyzine *in vivo* or administered de novo, would be inhibited by coadministration of cimetidine; (c) cimetidine would enhance the suppressive effect of hydroxyzine and cetirizine

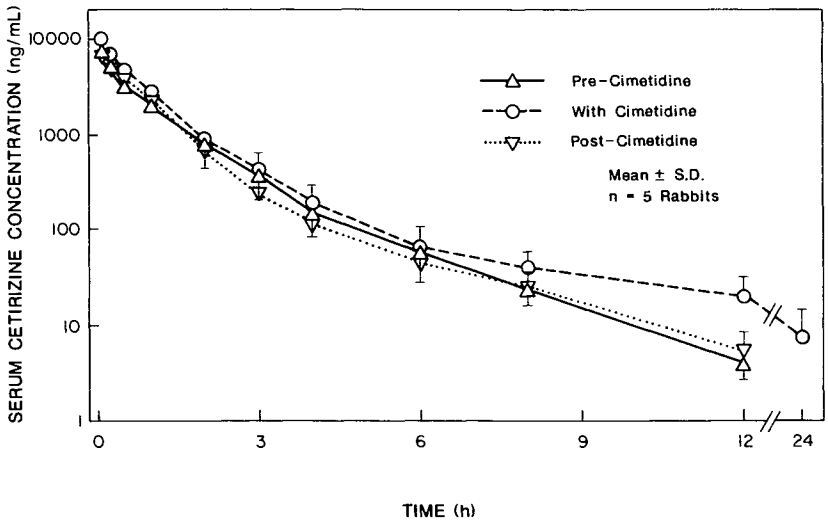

Fig. 3. Mean serum cetirizine concentration versus time plots after an intravenous injection of 10 mg cetirizine before, during, and after the coadministration of cimetidine.

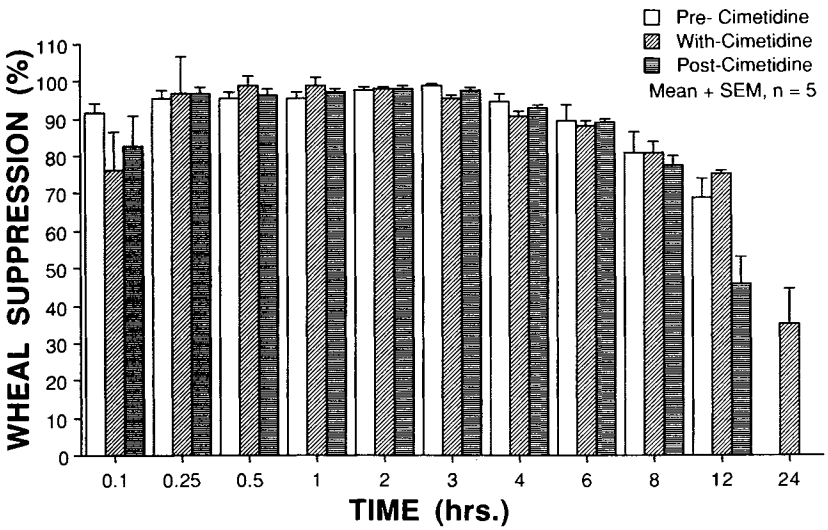

Fig. 4. Mean percent suppression of the histamine-induced wheals by hydroxyzine, 10 mg iv, before, during, and after the coadministration of cimetidine.

on the histamine-induced wheals; and (d) these effects would be reversible.

Cimetidine probably interferes with the elimination of hydroxyzine via inhibition of the hepatic cytochrome P_{450} mixed oxygenase system. The elimination of cetirizine arising from hydroxyzine appeared to be inhibited during cimetidine coadministration, as the $AUC_{0\rightarrow\infty}$ and C_{max} of cetirizine were significantly increased and the ratio of cetirizine $AUC_{0\rightarrow\infty}$ to hydroxyzine $AUC_{0\rightarrow\infty}$ (R) was increased. The inhibitory effect of cimetidine on the elimination of cetirizine was confirmed when cetirizine was administered de novo to the rabbits in Experiment B. Cetirizine is reported to be 50–80% excreted unchanged in the urine in rabbits (18). Cimetidine probably inhibits the elimination of cetirizine by competitively interfering with active tubular excretion of cetirizine in the kidney (10,11). The doses of cimetidine given were 50 times larger than the doses of hydroxyzine or cetirizine given; this ratio of H_1-antagonist/H_2-antagonist dose is similar to that used in patients receiving combination H_1- and H_2-antagonist treatment (10,11).

Histamine produces a wheal by increasing the permeability of the postcapillary venules and facilitating passage of plasma proteins and fluids into the extravascular spaces. Histamine-induced wheals were more than 90% suppressed after a single intravenous 10 mg dose of hydroxyzine, suggesting that hydroxyzine tissue concentrations and H_1-receptor saturation were high. Lower doses of hydroxyzine would have caused less wheal suppression but would also have resulted in lower serum hydroxyzine concentrations, making the pharmacokinetic analysis less reliable. Coadministration of cimetidine with concomitant increase in serum and, presumably, tissue hydroxyzine concentrations increased the amount of wheal suppression, but the increase was not statistically significant. The effectiveness of the hydroxyzine dose administered alone and the variability of this pharmacologic response among rabbits in the small num-

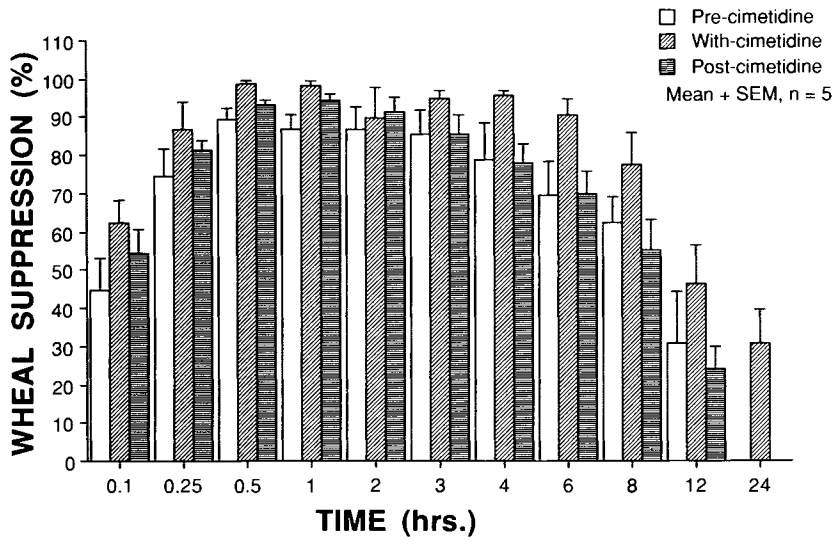

Fig. 5. Mean percent suppression of the histamine-induced wheals by cetirizine, 10 mg iv, before, during, and after the coadministration of cimetidine.

ber of animals may have contributed to our inability to detect a statistically significant effect of cimetidine coadministration on wheal suppression.

In the pharmacodynamic modeling process, two problems were encountered. First, although cetirizine is one-fourth as potent as hydroxyzine *in vitro,* the contribution of the cetirizine to the pharmacological effect of hydroxyzine cannot be ignored (6). A modified hydroxyzine concentration, obtained by adding one-fourth of the concentration of cetirizine to that of hydroxyzine, was therefore used in the pharmacodynamic calculations. Second, a large variability between rabbits was observed in pharmacological responses, as compared to a small degree of variability in serum hydroxyzine and cetirizine concentrations. In the presence of cimetidine, E_{max} values were larger, but the increase was not statistically significant.

It was not possible to demonstrate any significant effect of cimetidine alone in suppressing the histamine-induced wheals, as mean wheal areas after coadministration of cimetidine, 100 mg/kg twice daily for 1 week, 0.700 ± 0.150 cm^2, did not differ significantly from mean wheal areas at the beginning of the study before any medication had been administered, 0.676 ± 0.120 cm^2.

The data obtained by plotting the mean percentage suppression of the histamine-induced wheals versus mean serum cimetidine concentrations when cetirizine was administered de novo could not be fit to the pharmacodynamic E_{max} model (15,16). There was a lag in onset of maximum wheal suppression response relative to maximum serum cetirizine concentrations. Also, cetirizine produced persistent wheal suppression and even when serum cetirizine concentrations were decreasing, the histamine-induced wheal remained significantly suppressed. Eight hours after an intravenous dose of cetirizine, 10 mg, wheals were still 80% suppressed. After 12 hr, when wheal suppression was waning, serum cetirizine concentrations were undetectable, i.e., below 2 ng/mL.

Although wheal suppression was increased when cimetidine was coadministered with cetirizine, compared to the amount of wheal suppression observed precimetidine and postcimetidine, the differences were not statistically significant. We attribute this to the observation that cetirizine alone was highly effective in suppressing the histamine-induced wheals and that the cetirizine concentrations in the tissues were high enough to occupy all the H_1-receptors in the precimetidine phase of the study: Further increases in the serum cetirizine concentration and presumably in the tissue cetirizine concentrations did not result in more H_1-receptors being occupied. Lower doses of cetirizine would have compromised the reliability of the pharmacokinetic analysis. In addition to the small potential for increased receptor occupancy and enhanced efficacy, there was considerable variability.

In this rabbit model, we have demonstrated that cimetidine inhibits the elimination of hydroxyzine and the active metabolite of hydroxyzine, cetirizine, resulting in elevated serum concentrations of these H_1-antagonists during cimetidine coadministration. The increase in suppression of the histamine-induced wheals during cimetidine coadministration is therefore due, at least in part, to increased serum and tissue H_1-antagonist concentrations. A synergistic effect of H_1- and H_2-antagonists at the receptor level has not been excluded, and further studies of the mechanism of the enhanced efficacy of an H_1-antagonist during coadministration with an H_2-antagonist should be designed to test this possibility as well.

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