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Comparison of Vancomycin- and Teicoplanin-Induced Histamine Release and "Red Man Syndrome"

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Twelve healthy adult males participated in a double-blind, randomized, two-way crossover study to determine histamine release and the frequency and severity of "red man syndrome" (RMS) following intravenous administration of vancomycin (15 mg/kg of body weight over 60 min) and teicoplanin (15 mg/kg over 30 min). Concentrations of vancomycin and teicoplanin in serum and concentrations of histamine in plasma were measured at baseline and during and after each infusion. Erythema and pruritus were classified a priori as mild, moderate, or severe. The extent of erythema was determined by the use of a burn chart, and pruritus was assessed by the subject with a rank scale. Global severity of RMS was determined by summation of the individual scores for pruritus and erythema. Baseline areas under the concentration-time curve for histamine were not significantly different for the vancomycin and teicoplanin treatments. Vancomycin caused RMS in 11 of 12 subjects (9 severe and 2 moderate cases) and was associated with a significant increase in plasma histamine (46.7 ± 31.3 ng · min/ml, $P < 0.05$). In contrast, teicoplanin did not cause RMS or elicit significant histamine release (8.7 ± 13.2 ng · min/ml). Peak concentrations of vancomycin and teicoplanin in serum were 58.8 ± 8.4 and 148.0 ± 31.8 μg/ml, respectively ($P < 0.05$). Assuming equal efficacy, these data suggest that teicoplanin may be a safe alternative agent in subjects experiencing severe RMS due to vancomycin; however, further studies in the clinical setting are needed.

Vancomycin is widely used for the treatment of infections caused by gram-positive organisms. The most common adverse effect of intravenously administered vancomycin is "red man syndrome" which is characterized by erythema, pruritus, and in severe cases angioedema and cardiovascular complications (1, 3, 8, 10, 11, 15). We have previously shown that vancomycin-induced red man syndrome is associated with histamine release (13).

Teicoplanin is an investigational glycopeptide antibiotic similar in structure and spectrum of activity to vancomycin and is currently under study for the treatment and prophylaxis of infections due to gram-positive organisms (17, 18). There have been two anecdotal reports of teicoplanin-induced red man syndrome (B. Fant, personal communication); however, the frequency and severity of this reaction have not been systematically studied. The purpose of this investigation was to compare histamine release and the incidence and severity of red man syndrome following intravenous administration of vancomycin and teicoplanin to healthy adult volunteers.

MATERIALS AND METHODS

This study was approved by the Committee on the Conduct of Human Research, Medical College of Virginia Hospitals, and written informed consent was obtained from the participants. Subjects were admitted to the Biopharmaceutics Research Center, School of Pharmacy, Medical College of Virginia, on the morning of each study day.

Volunteers. Twelve healthy adult, Caucasian, male volunteers participated in a double-blind, randomized, two-way crossover study. There was a 2-week washout period between treatments. The mean ± standard deviation age and weight were 24.1 ± 1.2 years and 76.9 ± 5.5 kg, respectively. Exclusion criteria for subjects were previous exposure to vancomycin and/or teicoplanin, smoking, total body weight more than 10% above or below ideal weight, known hypersensitivity to any drug, chronic illnesses, atopy, laboratory abnormalities on entry into the study, requirements for any medication, and use of antihistamine-containing products within 7 days prior to entering the study. Subjects were instructed to avoid all medications throughout the study period. No subject ingested alcohol or caffeine 48 h prior to each study day, and subjects fasted overnight and for 3 h after administration of each antibiotic.

Drug administration and sample collection. All antibiotic doses were prepared by the same investigator (D.P.H.). Teicoplanin was supplied by Merrell Dow Research Institute, Cincinnati, Ohio (lot IC3960), as a dry sterile, lyophilized powder (200 mg per vial) for reconstitution and intravenous administration. For injection, the powder was reconstituted with sterile water according to the recommendations of the manufacturer and filtered through a 5-μm filter needle. Vials were rinsed once to remove any residual drug, and the final dose (15 mg/kg of body weight) was diluted to 100 ml with 0.9% sodium chloride (USP). Doses of vancomycin (Vancocin, lot 2MS01A; Eli Lilly & Co., Indianapolis, Ind.) were aseptically prepared according to the instructions in the package insert. For injection, the drug was reconstituted with sterile water as described in the package insert and filtered through a 5-μm filter needle. Vials were rinsed once to remove any residual drug.

The recommended infusion durations of teicoplanin and vancomycin are 30 and 60 min, respectively. In order to maintain blinding, two sequential infusions, each 30 min in duration, were given in each arm of the subject. When teicoplanin was scheduled to be administered, each subject

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first received a 30-min infusion of 0.9% sodium chloride (USP), followed by teicoplanin (15 mg/kg) administered as a 30-min infusion. Vancomycin was administered as two separate 30-min infusions (7.5 mg/kg each; 15 mg/kg total). At the end of the teicoplanin and vancomycin infusions (60 min), the lines were flushed with 20 ml of 0.9% sodium chloride to ensure total drug delivery. Each infusion bag was covered by an opaque plastic cover, and all manipulations were carried out by an unblinded investigator (D.P.H.). The entire infusion apparatus was obscured from the view of subjects and blinded investigators.

Indwelling intravenous catheters (Cathlon IV; Critikon, Tampa, Fla.) were inserted into each forearm of a subject 1 h prior to the start of the infusion. One catheter was used for infusion of the antibiotic, and the second catheter (in the contralateral arm) was used for the procurement of blood. Patency of the indwelling catheters was maintained by frequent flushing with 2 ml of normal saline. Serial blood samples were obtained to determine histamine concentrations in plasma at the following times: 60, 30, and 0 min prior to infusion (baseline samples); during the infusion at 10, 20, 30, 40, 50, and 60 min (end of infusion); and at 5, 10, 15, 30, 60, and 120 min after the infusion. Subjects returned 24 h after the start of the infusion to have a final sample collected for antibiotic and histamine determinations. Blood samples used to determine vancomycin and teicoplanin concentrations were collected in empty evacuated glass tubes, and samples for histamine determinations were placed into cold evacuated glass tubes containing 0.04 ml of 15% EDTA solution. Blood samples were immediately placed on ice for approximately 30 min. Sera and plasma were separated by centrifugation (1,500 × *g*) at 3,000 rpm for 10 min and stored at −70°C until time of assay (within 4 weeks).

Assay methodology. Histamine concentrations in plasma were determined by a radioimmunoassay (Histamine, lot 46; AMAC Inc., Westbrook, Maine). This assay has been shown to produce results equivalent to those produced by the radioenzymatic assay (9). The sensitivity of the assay is 0.25 ng/ml. Prepared standard curves were linear over the range of 0.25 to 5 ng/ml. The within-day and between-day coefficients of variation of controls for the concentration of 5.0 ng/ml were <10%. The within-day and between-day coefficients of variation at 0.25 ng/ml were 12 and 16%, respectively. Assays were performed by one blinded investigator (J.S.).

Vancomycin concentrations in serum were determined by a fluorescence polarization immunoassay procedure (TDx; Abbott Diagnostic, Div. Abbott Laboratories, Irving, Tex.). The assay has a sensitivity limit of 0.6 μg/ml, with reported within-day and between-day coefficients of variation of less than 5% in the concentration range of 0.6 to 100 μg/ml (12).

Teicoplanin concentrations in serum were determined by the Merrell Dow Research Institute by using an agar diffusion microbiological assay with *Bacillus subtilis* ATCC 6633 (Difco Laboratories, Detroit, Mich.) as the test organism (4). The sensitivity of the assay is 0.2 μg/ml. Standards were prepared in pooled human serum, and samples were run in six replicates. The within- and between-day coefficients of variation were <10%, and the assay was linear over the range of 0.2 to 96 μg/ml. Samples containing concentrations greater than 96 μg/ml were diluted in blank, pooled serum and reassayed.

Calculations. Basal production of histamine for the 3 h preceding the infusion was estimated by using the linear trapezoidal rule to calculate the area under the concentration-time curve (AUC) from concentrations in plasma at −1.0, −0.5, and 0 h and multiplying this value by three. To estimate the quantity of histamine released into plasma with each treatment, the total AUC from the beginning of the infusion to 3 h after beginning the infusion was calculated by using the linear trapezoidal rule. Basal AUC_{-3-0} was then subtracted from the total AUC; the difference represents the histamine released (AUC_{0-3}). The AUCs for vancomycin and teicoplanin from the beginning of the infusion to 3 h were also calculated by using the trapezoidal rule.

Evaluation of red man syndrome. During each infusion, subjects were evaluated for the presence of signs and symptoms consistent with red man syndrome. A blinded investigator (J.S. or M.S.) evaluated the same subjects during the two treatment periods. Supine blood pressure, heart rate, and respiration were measured immediately after each blood sample collection. The methods of determining extent of erythema, degree of pruritus, and global severity of red man syndrome are described below.

Erythema. The area of erythema (determined by the subject and confirmed by the investigator) was drawn onto a burn chart, cut out, weighed, and expressed as a percentage of the total weight of the chart. The area of erythema was expressed as a percentage of total body surface area (BSA) and converted to the following ordinal scale: less than 1% BSA (score of 0, no reaction), 1 to 5% BSA (score of 1, mild), 5 to 10% BSA (score of 2, moderate), and greater than 10% BSA (score of 3, severe). Photographs of the face and upper torso of each subject were taken before each infusion and subsequently with the development of erythema.

Pruritus. Intensity of itching was determined by the subject and classified a priori by a previously described method (7) as no reaction (score of 0), mild (score of 1), moderate (score of 2), and severe (score of 3).

Global severity. A global score for red man syndrome was calculated from the sum of the individual scores for pruritus and erythema, according to the following scale: no reaction (total score of 0), mild (total score of 1 to 2), moderate (total score of 3 to 4), and severe (total score of 5 to 6). For example, a subject with an erythema score of 3 and a pruritus score of 2 would receive a global score of 5 and be classified as having severe red man syndrome.

Statistical analysis. A sample size of 12 subjects was prospectively estimated by using the following assumptions: an 80% expected frequency of red man syndrome in the vancomycin group (estimated from reference 13), a syndrome frequency of 20% in the teicoplanin group, a beta error of 0.2, and a two-tailed alpha of 0.05 (16). Differences between the two treatments regarding severity of erythema, pruritus, and red man syndrome, and AUCs for histamine were determined by the signed rank test. Differences in the AUCs for vancomycin and teicoplanin were evaluated by the Student paired *t* test. Comparisons of interval data from between treatments are expressed as means ± standard deviations. Relationships between histamine and reaction severity were evaluated by the Spearman correlation coefficient. Statistical significance was established when P values were <0.05.

RESULTS

On the basis of their global scores, 11 of 12 subjects (92%) experienced red man syndrome while receiving vancomycin. Nine of these reactions were considered severe, and two were of moderate severity. One subject had no reaction. Erythema and pruritus generally developed together, an average of 25 ± 11 min after the infusion was started. The

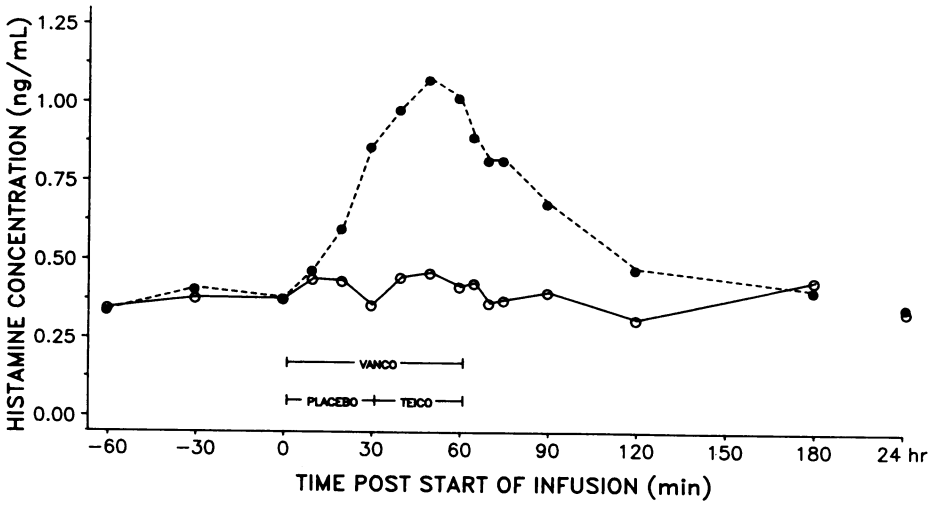

FIG. 1. Mean histamine concentrations in subjects receiving vancomycin (VANCO) (●) and teicoplanin (TEICO) (○). Time zero is the beginning of each infusion.

mean duration of pruritus was 70 ± 20 min after onset. Two subjects who experienced severe reactions also complained of tingling of the lips and headaches during the infusion. In addition, one subject complained of mild chest pains which lasted 30 min during the infusion. This subject also experienced tachycardia (baseline, 60 beats per min, increasing to 96 beats per min at the end of the infusion). There was no change in his blood pressure or respiratory rate. No other subject experienced cardiovascular or respiratory changes. One subject requested that the vancomycin infusion be terminated five min early because of excessive itching. His reaction started 15 min into the infusion, became severe at 30 min and resolved 70 min after the infusion was stopped.

Baseline $AUCs_{-3-0}$ for histamine not significantly different between the vancomycin and teicoplanin treatment groups (68.9 ± 17.6 and 66.3 ± 18.5 ng · min/ml, respectively). The development of vancomycin-induced red man syndrome in all cases was accompanied by an increase in histamine concentrations in plasma, which subsequently returned to baseline levels within 1 h after discontinuation of the infusion (Fig. 1). AUC_{0-3} for histamine in subjects receiving vancomycin was 113.5 ± 40.1 ng · min/ml ($P < 0.001$ compared with baseline). After corrections for baseline were made, AUC_{0-3} for histamine was 46.7 ± 31.3 ng · min/ml. There was a significant correlation between the AUC_{0-3} for histamine and severity of erythema ($r = 0.73$, $P = 0.015$); no correlation existed for histamine AUC and pruritus ($r = 0.19$, $P = 0.52$). Likewise, there were significant correlations between peak histamine concentration and global severity ($r = 0.61$, $P = 0.044$; Fig. 2) and peak histamine concentration and erythema severity ($r = 0.63$, $P = 0.03$). Pruritus was not significantly correlated.

In contrast, no subject experienced histamine release or red man syndrome as a result of teicoplanin administration. One subject did experience mild erythema and pruritus for 10 min beginning 5 h after the teicoplanin infusion. Although these symptoms may have been caused by teicoplanin, we did not classify this as a red man syndrome since signs and symptoms of vancomycin-induced red man syndrome have occurred during or shortly after the infusion in all subjects reported to date. In subjects receiving teicoplanin, AUC_{0-3} for histamine was 70.2 ± 23.8 ng · min/ml ($P > 0.05$ compared with baseline). Corrected for baseline values, AUC_{0-3} was 8.7 ± 13.2 ng · min/ml. There were no other adverse effects.

Peak concentrations of vancomycin and teicoplanin in serum were 58.8 ± 8.4 and 148 ± 31.8 μg/ml, respectively (Fig. 3). Mean AUC_{0-24} for teicoplanin was also significantly higher than that for vancomycin (184.0 ± 35.0 versus 96.6 ± 13.2 μg · h/ml, $P < 0.05$). When the mean change in histamine concentration is plotted versus mean drug concentration, a close relationship is observed for vancomycin, whereas no relationship is observed for teicoplanin (Fig. 4). These data suggest the existence of a threshold concentration of vancomycin which may be necessary for histamine release.

DISCUSSION

Consistent with our previous studies in normal volunteers (6, 13, 14), vancomycin caused a high incidence of red man syndrome. Particularly noteworthy in the present investigation was the high number of reactions classified as severe (9 of 12 [75%]), which necessitated discontinuation of the

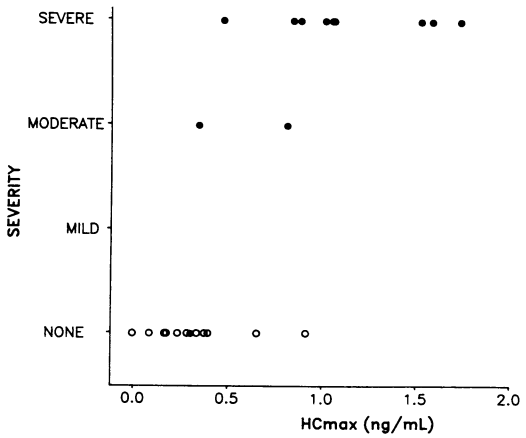

FIG. 2. Correlation between peak concentrations of histamine (HCmax) in plasma and global reaction severity for subjects receiving vancomycin (●) and teicoplanin (○). Spearman's rank correlation coefficient was 0.61 ($P = 0.044$).

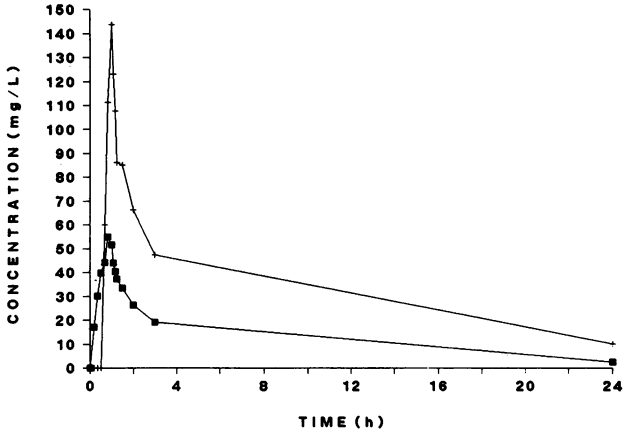

FIG. 3. Plot of mean concentrations of vancomycin (■) and teicoplanin (+) in serum versus time.

infusion in one individual. The most likely explanation is that the dose in this study was normalized for body weight (15 mg/kg), which resulted in an average administered dose of 1,154 ± 83 mg. In contrast, our previous investigations used a dose of 1,000 mg, irrespective of the body weight of the individual. Thus, the total dose and therefore the rate of infusion in this study were higher than in previous studies. Possible reasons for the high incidence of red man syndrome in normal individuals have been previously discussed (13). In a recent prospective investigation of patients who received 1,000 mg of vancomycin infused over 1 h, 8 of 17 individuals (47%) developed red man syndrome, suggesting that a high incidence of this reaction is not confined to normal healthy adults (M. R. Wallace, J. Mascola, and E. C. Oldfield, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 648, 1989).

In this study, vancomycin-induced red man syndrome was associated with histamine release into plasma; both AUC and peak concentrations of histamine in serum showed a significant correlation to severity of erythema and global score. However, the correlation between histamine and pruritus was not significant, possibly reflecting the subjective nature of pruritus and thus greater error in measurement. Some subjects demonstrated marked reactions associated with relatively modest release of histamine, whereas others demonstrated the opposite relationship. Thus, although histamine is probably a mediator in this reaction, other mediators may also be involved. In addition, some subjects may have increased receptor sensitivity to histamine; thus, they experience more-severe reactions with a relatively small amount of histamine release. Despite marked histamine release, cardiovascular symptoms were observed in only one subject. Possible reasons for this include the fact that our subjects were young, healthy volunteers on no other medications and were in a recumbent position during the infusions.

Teicoplanin is active in vitro against gram-positive organisms (17, 18) and is currently being evaluated in clinical trials to determine its efficacy and toxicity profile. Most published studies have used a daily dose of 4 to 6 mg/kg. However, these doses have been associated with treatment failures (2, 5, 18). Currently, a dose of 15 mg/kg is being evaluated in clinical trails (J. Heilman, personal communication), and this provided the rationale for the dose used in this study. Although teicoplanin was administered at twice the rate of vancomycin, resulting in higher levels in serum, teicoplanin did not cause histamine release or red man syndrome in this study. Possible explanations are that the structure of teicoplanin may differ sufficiently from that of vancomycin to prevent binding to the receptors responsible for histamine release and that since teicoplanin is highly protein-bound (90%) (17), there may be insufficient free drug to bind to the receptor for histamine release.

In subjects experiencing vancomycin-induced red man syndrome, increasing the duration of infusion (6) and/or pretreatment with an H1 antagonist (14) may be effective in ameliorating the symptoms. Alternatively, if teicoplanin proves to be efficacious in treating serious staphylococcal infections at a dose of 15 mg/kg or less, this study suggests that it may be a safe alternative agent in patients unable to tolerate vancomycin-induced release of histamine. Although it is presumed that the mechanism of red man syndrome is

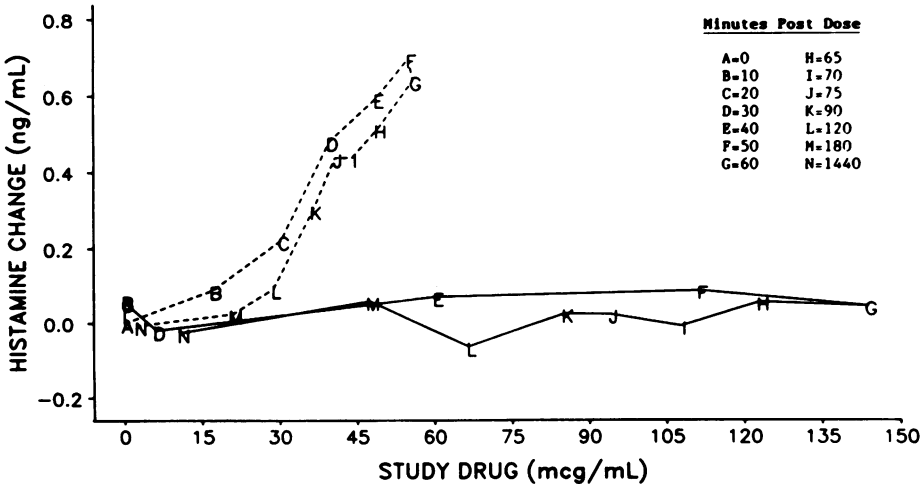

FIG. 4. Plot of the mean change in histamine concentrations after infusion of antibiotics was started (postinfusion times are indicated in the figure as a function of the corresponding mean concentrations of vancomycin (– – –) and teicoplanin (——). On average, the rise and fall of histamine concentrations paralleled those of vancomycin. Teicoplanin did not cause a change in histamine, even at the highest concentration of drug.

the same for healthy volunteers and patients, the possibility remains that a patient who has experienced severe red man syndrome with vancomycin may also experience red man syndrome with teicoplanin. Clinical experience in such patients will be important to determine the ultimate role of teicoplanin.

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