Vancomycin-Induced Histamine Release and "Red Man Syndrome": Comparison of 1- and 2-Hour Infusions

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Vancomycin-induced "red man syndrome" (RMS) is mediated in part by histamine release, and its severity is correlated with the area under the plasma histamine concentration-time curve. Ten adult male volunteers participated in a randomized, double-blind, two-way crossover trial (1-week washout interval between regimens) to determine the effect of 1- and 2-h infusions of vancomycin (1.0 g) on histamine release and on the frequency and severity of RMS. The severity of RMS was classified as mild, moderate, or severe from a combined score of pruritus and extent of erythema. Serial concentrations of histamine in plasma and concentrations of vancomycin in serum were measured at baseline and during and after each infusion. Of 10 subjects, 8 had evidence of RMS during the 1-h infusion (3 mild, 3 moderate, and 2 severe), whereas only 3 of the 10 subjects (all mild) had RMS during the 2-h infusion (P < 0.05). The 1-h infusion was associated with a significantly greater peak concentration of histamine in plasma (1.8 ± 0.7 versus 1.0 ± 0.6 ng/ml, P = 0.004) and a greater total release of histamine (74.3 ± 54.1 versus 36.4 ± 22.6 ng·min/ml, P = 0.017) than was the 2-h infusion. These data suggest that administration of vancomycin over 2 h reduces the frequency and severity of RMS and the amount of histamine released compared with those after a 1-h infusion in healthy volunteers.

The rising incidence of infections caused by methicillin-resistant strains of staphylococci has led to an increase in the use of vancomycin. The most common adverse effect of intravenously administered vancomycin is a constellation of signs and symptoms known as "red man (red-neck) syndrome" (RMS). This syndrome is characterized by pruritus; erythema of the face, neck, and upper torso; and in severe cases, angioedema and cardiovascular collapse (4, 7, 19, 21). Vancomycin-induced RMS is mediated in part by histamine release, and its severity is correlated with the area under the plasma histamine concentration-time curve (AUC) (13, 21, 22). RMS in infected patients and healthy volunteers is generally associated with rapid administration of vancomycin (<30 min; 1, 4, 7, 16, 21, 24); however, the reaction has been reported to occur with prolonged infusions (5, 19).

Data from our previous investigations and from other centers indicate that the incidence of RMS in healthy volunteers receiving 1.0 g of vancomycin over 60 min is about 80 to 95% (1, 12, 21, 22; J. Sahai, D. P. Healy, M. J. Shelton, J. S. Miller, and R. Polk, submitted for publication). The true incidence of vancomycin-induced RMS in infected patients is currently unknown; however, RMS is generally thought to occur less commonly in infected patients than in volunteers. Despite these potential differences between volunteers and patients, the clinical manifestations in both populations are similar, suggesting a common responsible mechanism(s).

Since the rate of infusion is thought to be an important determinant in RMS, a logical step to avoid the reaction would be to increase the duration of infusion. Therefore, the purpose of this study was to evaluate 1- and 2-h infusions of vancomycin (1.0 g) with respect to histamine release and frequency and severity of RMS in normal volunteers.

This work has been presented before (90th Annu. Meet. Am. Soc. Clin. Pharmacol. Ther., Nashville, Tenn., 10 March 1989, abstr. no. III C-11.)

MATERIALS AND METHODS

The study protocol was approved by the Medical College of Virginia Committee on the Conduct of Human Research, 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. Ten healthy adult Caucasian male volunteers participated in a randomized, double-blind, two-way crossover study. Seven subjects were vancomycin naive at the time of study, whereas three had previously received vancomycin during a similar study 2 weeks earlier. These three subjects were included to permit gross evaluation of the variability of histamine release and of reaction severity under the same experimental conditions on two separate occasions. The mean (± standard deviation) age and weight were 24.6 ± 2.3 years and 77.4 ± 8.5 kg, respectively. Volunteers were excluded on the basis of the following criteria: hypersensitivity to any drug, smoking, total body weight deviating more than 10% from ideal weight, showing laboratory abnormalities on prescreening, having chronic illnesses or requiring any medication, and ingesting antihistamine-containing products within 2 weeks of study participation. Subjects were instructed to avoid all medications throughout the study period and to abstain from alcohol and caffeine beginning 48 h before each of the two study days. Subjects fasted overnight and for 3 h after vancomycin administration.

Drug administration and sample collection. All doses of vancomycin were prepared by the same investigator (S.F.). Vials containing 0.5 g of vancomycin hydrochloride (Vancocin; lot ONZ54B; Eli Lilly & Co., Indianapolis, Ind.) were
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as practiced according to the instructions of the manufacturer (Vancocin package insert; Eli Lilly & Co., Indianapolis, Ind., 1986). The drug was reconstituted with sterile water for injection and filtered through a 0.5-μm pore-size filter. Vials were rinsed with 10 ml of sterile water for injection to remove drug residue. The resultant volume was diluted with sufficient 5% glucose in water to produce a final volume of 200 ml for each 1-g dose.

Doses of vancomycin were administered as 1- and 2-h continuous intravenous infusions with a precalibrated volumetric infusion device (Travenol 8000 volumetric pump; Travenol Laboratories, Morton Grove, Ill.). To preserve binding of subjects and investigators, each dose appeared to be infused over a 2-h period. One-hour infusions consisted of vancomycin infusion over the first hour followed by a 60-min infusion of normal saline. Two-hour infusions consisted of vancomycin only. At the end of each infusion, the administration lines were flushed with 20 ml of 0.9% sodium chloride to ensure total drug delivery. The entire infusion apparatus (i.e., pump and infusate) was obscured from the view of the subjects and the blinded investigators. Manipulations of the infusion pump (e.g., setting infusion rates and flushing administration lines) were done by an unblinded investigator (D.H.). There was a 1-week washout interval between treatments.

Indwelling intravenous catheters were inserted into both forearms 1 h before the start of the infusion. One catheter was used for the infusion of vancomycin, and a second catheter (in the contralateral arm) was used for the procurement of blood. Patency of the indwelling catheters was maintained with saline flushes.

Serial blood samples for histamine concentrations in plasma and vancomycin concentrations in serum were obtained at the following times for both regimens: 0.5 and 0.08 h before infusion (baseline samples); during the infusion at 0.25, 0.5, 1, 1.08, 1.25, 1.5, 1.75, and 2 h (end of infusion); and at 0.08, 0.25, 0.5, 0.75, and 1 h postinfusion. Additional samples for vancomycin concentration were obtained at 4, 6, 8, 10, 12, and 24 h postinfusion. Blood samples for vancomycin concentrations were collected in evacuated glass tubes, and those for histamine concentrations were collected in cold evacuated glass tubes containing 0.4 ml of 15% EDTA solution. Blood samples were immediately placed on ice for approximately 30 min. Serum and plasma were stored at −70°C until time of analysis (about 4 weeks).

**Assay methodology.** Histamine concentrations in plasma were determined by a radioimmunoassay (Histamine; lot 36; AMAC Inc., Westbrook, Maine) by the same blinded investigator (J.S.; 14). 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, with coefficients of variation of <1%.

Vancomycin concentrations in serum were determined by a fluorescence polarization immunooassay technique (TDx; Abbott Laboratories, Diagnostics Division, Irving, Tex.). The assay has a sensitivity of 0.6 μg/ml, with reported within-day and between-day coefficients of variation of <5% over the concentration range of 0.6 to 100 μg/ml (20).

**Kinetic and dynamic parameters.** The following parameters were determined by visual inspection of the data: maximum concentrations of histamine in plasma (C_{max,h}) and vancomycin in serum (C_{max,v}); times of maximum histamine (T_{max,h}) and vancomycin (T_{max,v}) concentrations; vancomycin concentrations at 1 and 12 h postinfusion. The total AUC from beginning of the infusion to 3 h after was calculated using the linear trapezoidal rule (8). Basal production of histamine for the 3 h preceding the infusion was estimated by taking the average baseline plasma concentration for each subject and multiplying this value by three (AUC_{3,0}). To estimate the quantity of histamine released into plasma from each regimen (AUC_{3,0}), the AUC_{3,0} was subtracted from the AUC. The AUC of vancomycin from 0 to 12 h (AUC_{0,12}) was calculated using the trapezoidal rule.

**Evaluation of RMS.** Subjects were evaluated for the presence of signs and symptoms consistent with RMS such as erythema, pruritus, and angioedema. A blinded investigator (J.S. or S.F.) evaluated the same subjects during the two treatment periods. Color photographs were taken of the faces, necks, and upper torsos of the subjects before each infusion and subsequently, when the development of any erythematos reaction became apparent to the investigator and subject. In addition, both supine blood pressure and heart rate were measured immediately after each blood sample collection. The methods for determining the extent of erythema, degree of pruritus, and global severity of RMS are described below.

(i) **Erythema.** The area of erythema (determined by the investigator and confirmed by the subject) was outlined onto a standard burn chart, cut out, weighed, and expressed as a percentage of total weight of the chart. The area of erythema was then expressed as a percentage of total body surface area (BSA) involved and was converted to the following ordinal scale: <1% BSA, score of 0, no reaction; 1 to 5% BSA, score of 1, mild reaction; 5 to 10% BSA, score of 2, moderate reaction; >10% BSA, score of 3, severe reaction.

(ii) **Pruritus.** The intensity of itching was determined by the subject and classified a priori according to a previously described scale (11) as follows: no reaction, score of 0; mild reaction, score of 1; moderate reaction, score of 2; and severe reaction, score of 3.

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

**Statistical analysis.** A sample size of 10 was prospectively estimated based on the following assumptions: an expected minimum frequency of RMS of 70% in the group receiving vancomycin over 1 h (estimation based on data from references 21 and 22), frequency of RMS reduced to 30% with a 2-h infusion, a beta error of 0.2, and a one-sided alpha of 0.05 (25). Differences between the two treatments regarding severity of global RMS were determined with the Wilcoxon signed-rank test. Continuous data were evaluated with Student's t test for paired data. Interval data are expressed as means ± standard deviations. The relationships between histamine release (AUC_{0,3}) and percent erythema and between AUC_{0,3} and C_{max,v} were evaluated by Pearson's correlation coefficient. Statistical significance was defined as P < 0.05.

**RESULTS**

Of 10 subjects, 8 had evidence of RMS based on their global score while receiving vancomycin as a 1-h infusion, whereas 3 of 10 showed evidence of RMS during the 2-h infusion (P < 0.05). Of the eight subjects with RMS after the 1-h infusion, four had received that regimen during study week 1, and four had received it during week 2. Erythema
was present in all subjects who experienced RMS, whereas pruritus was present in 6 of 10 subjects receiving the 1-h infusion and 2 of 10 subjects receiving the 2-h infusion. The global reaction severity was classified as mild in three, moderate in three, and severe in two subjects receiving the 1-h infusion, whereas it was classified as mild in all three subjects experiencing RMS during the 2-h infusion. Of those three subjects who developed mild RMS with the 2-h infusion, two experienced severe reactions and the other experienced a mild reaction with the 1-h infusion. The time of onset of erythema (a more objective parameter) was $41 \pm 11$ min for the 1-h infusion ($n = 8$) and $62 \pm 20$ min for the 2-h infusion ($n = 3$). Complete resolution of erythema occurred within 10 to 60 min after termination of both the 1- and 2-h infusions. No subject receiving either treatment experienced significant changes in supine blood pressure or heart rate during the infusion period or for 2 h after the end of infusion (data not shown).

Mean concentrations of histamine in plasma for the 1- and 2-h vancomycin infusions are shown in Fig. 1. The curves suggest a temporal relationship between the onset and resolution of erythema (see above) and the rise and fall of plasma histamine concentrations. $C_{\text{max}}$ values were $1.8 \pm 0.7$ ng/ml for the 1-h infusion and $1.0 \pm 0.3$ ng/ml for the 2-h infusion ($P = 0.025$). Corresponding values for $T_{\text{max}}$ for 1- and 2-h infusions were $1.0 \pm 0.3$ and $1.5 \pm 0.7$ h ($P = 0.016$), respectively. Baseline histamine AUC$_{0-3}$ values were not significantly different between the 1- and 2-h infusions ($52.6 \pm 18.9$ versus $48.0 \pm 24.1$ ng · min/ml; $P = 0.5$). Histamine release occurred with both regimens ($P < 0.0001$); however, it was significantly greater for the 1-h infusion than for the 2-h administration ($74.3 \pm 54.1$ versus $38.2 \pm 19.9$ ng · min/ml; $P < 0.02$) (Fig. 2). The mean increase in histamine AUC$_{0-3}$ above baseline were 127 and 99% for the 1- and 2-h infusions, respectively. Despite histamine release in all subjects experiencing RMS, there was no significant correlation between the amount of histamine released into plasma and the extent of erythema ($r = 0.29$; $P > 0.2$).

Mean vancomycin-concentration-versus-time profiles after a single 1.0-g dose administered over 1 and 2 h are illustrated in Fig. 3. Mean concentrations of vancomycin in serum at the end of infusion, at 1 h postinfusion, and at 12 h postinfusion were $51.1 \pm 9.2$ (1 h) versus $37.6 \pm 3.6$ (2 h) µg/ml, $24.9 \pm 2.9$ (1 h) versus $21.2 \pm 2.2$ (2 h) µg/ml, and 3.9 ± 0.8 (1 h) versus 4.4 ± 0.8 (2 h) µg/ml, respectively. The vancomycin AUC$_{0-12}$S were $167.5 \pm 21.5$ µg · h/ml for the 1-h infusion and $167.0 \pm 18.5$ µg · h/ml for the 2-h infusion ($P > 0.5$).

**DISCUSSION**

The high incidence of vancomycin-induced RMS in the present study is consistent with our previous findings (21, 22; Sahai et al., submitted for publication) and those from other centers (1, 12) in which volunteers received 1.0 g of vancomycin over 1 h. Infusion of vancomycin over 2 h resulted in significant decreases in the frequency and severity of RMS and in the amount of histamine released into plasma compared with results after a 1-h infusion. These data confirm the widely held belief that rate of infusion is an important determinant of RMS.

There was no significant relationship between histamine AUC and either overall severity of reaction or extent of erythema (the most objective response parameter), despite considerable histamine release in all subjects with RMS. This is in contrast to our two previous investigations (21, 22).

**FIG. 1.** Mean ± standard deviation histamine concentration-versus-time profile for volunteers receiving 1.0 g of vancomycin administered as 1-h (■) and 2-h (○) infusions.

**FIG. 2.** Illustration of histamine AUC after administration of 1.0 g of vancomycin over 1 and 2 h. AUC is corrected for basal concentrations to reflect amount of histamine released for each subject (■) (see Materials and Methods). Symbol: □, mean AUC.

**FIG. 3.** Mean ± standard deviation vancomycin concentrations in serum after administration of a single dose of 1.0 g infused over 1 h (■) and 2 h (○).
This discrepancy may be related to the relatively small sample size employed and may have been further confounded by three subjects having prior exposure to vancomycin in a separate study. Two of these subjects experienced RMS of moderate severity in the previous study (using similar methods), whereas neither of them exhibited a reaction in the present study. The third subject experienced severe RMS in the first trial but only a mild reaction in the present study. All three subjects had significant histamine release (AUC) in both investigations. These data suggest at least two possibilities: histamine end-organ receptors become desensitized because of prior vancomycin exposure and/or other mediators and cofactors such as serotonin, bradykinin, slow reactive substance of anaphylaxis (SRS-A), cyclic GMP, and PGD_2 are also involved. In addition, individual differences in histamine receptor sensitivity may explain why some individuals had large amounts of histamine released without significant reaction.

There was no linear relationship between C_{max,v} (r = 0.33; P = 0.34) or AU_{0-3} of vancomycin (r = 0.39; P = 0.27) and histamine release. The interrelationships between vancomycin concentrations in serum and tissue, "vancomycin receptors" on basophils and mast cells, histamine concentrations, histamine receptors, and the occurrence of RMS are complex and appear to differ greatly between individuals. Rate-response studies and pharmacodynamic modeling of vancomycin and histamine concentration-time data may help elucidate these concentration-effect relationships.

Extrapolating data from healthy volunteers to hospitalized patients is difficult because of inherent differences between the two populations. The presence of bacteria (3, 6, 17), malignancy (2), diabetes (10), or various medications (e.g., antihistamines [22]) has been shown to alter the normal release of or response to histamine in an individual. As a result, patients with disease may have a lower reaction rate and less severe RMS compared with healthy volunteers or uninfected patients receiving vancomycin for prophylaxis (1, 4, 7, 12, 18, 23, 24). Collectively, these data suggest the observation that RMS occurs less frequently in hospitalized patients than in healthy volunteers. However, a recent prospective study in infected patients reported an overall reaction frequency of 24%; the reaction rate was 47% when those receiving concomitant antihistamines were excluded (M. R. Wallace, J. Mascola, and E. C. Oldfield, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 648, 1989). Irrespective of differences in reaction frequency, RMS is reported to be the most common adverse effect of vancomycin administration in volunteers and patients, and signs and symptoms of the reaction are similar in both populations (5, 7, 19, 21).

Our data derived from volunteers indicate that administration of vancomycin over 2 h reduces the frequency and severity of RMS and the amount of histamine released compared with the results of a 1-h infusion. Until further studies are completed in specific patient populations, we recommend increasing the duration of infusion to 2 h in those who experience RMS with a 60-min infusion. Peak concentrations of vancomycin in serum 1 h after a 2-h infusion are not appreciably different from those 1 h after a 1-h infusion. Therefore, the same range of 25 to 40 μg/ml can be used as a guide for monitoring peak concentrations if such monitoring is deemed necessary (9, 15). In addition, trough concentrations and AUCs of vancomycin are similar for 1- and 2-h infusions.

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LITERATURE CITED