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Absence of "Red Man Syndrome" in Patients Being Treated with Vancomycin or High-Dose Teicoplanin

MICHAEL J. RYBAK,[1-3]* ELAINE M. BAILEY,[1-3] AND LAWRENCE H. WARBASSE[1,4]

College of Pharmacy and Allied Health Professions[1] and Division of Infectious Diseases, Department of Medicine,[2] Wayne State University, Detroit, Michigan 48201, and The Anti-Infective Research Laboratory, Department of Pharmacy,[3] and Department of Medicine,[4] Detroit Receiving Hospital and University Health Center, Detroit, Michigan 48201

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Twenty-five febrile patients with a history of intravenous drug use who were receiving either vancomycin (15 patients) or teicoplanin (10 patients) as part of a multicenter, double-blind, randomized, clinical efficacy trial were enrolled, upon receipt of their first dose of antibiotic, into a study to evaluate the effect of 1 g of vancomycin and high-dose teicoplanin (30 mg/kg of body weight) on histamine release and the occurrence of "red man syndrome" (RMS). In addition, 10 healthy volunteer subjects (HVS) were randomized to receive either 1 g of vancomycin intravenously or a saline infusion in a double-blind, crossover design study. Patients and HVS were observed for the presence of erythema, flushing, pruritus, and hypotension during and for up to 1 h postinfusion by a blinded investigator. Histamine concentrations in plasma were measured at baseline and during and after drug infusion. No significant differences were noted in baseline temperature between patients (vancomycin recipients, 102.3°F [39.1°C]; teicoplanin recipients, 102.4°F [39.1°C]) or incidence of bacteremia (7 of 15 vancomycin recipients; 5 of 10 teicoplanin recipients). There were no significant differences in peak vancomycin concentrations in the sera of patients (40.8 μg/ml) and HVS (49.9 μg/ml). There were no reactions consistent with RMS in any patient who received teicoplanin (0 of 10); there was a significant difference in the occurrence of RMS in patients in comparison with that in HVS (0 of 15 patients, 9 of 10 HVS; $P < 0.001$) who received vancomycin. The predominant reaction was erythema and pruritus. Histamine concentrations in plasma and the area under the histamine plasma concentration-time curve were highly variable within groups and were not statistically different between patients and HVS. The incidence of RMS secondary to vancomycin or teicoplanin in our patient population appears to be low and consistent with clinical observations. Similar to previous investigations, RMS secondary to vancomycin in HVS was high (90%). However, we found no relationship between the histamine concentration in plasma or the area under the plasma histamine concentration-time curve and the severity of RMS in HVS. The reason for the discrepancy of RMS in patients versus that in HVS is unknown, but it may be related to a blunted effect of glycopeptides to produce the reaction in the presence of infection or it may be specific to our patient population.

Vancomycin is a glycopeptide antibiotic that has been in clinical use for more than 37 years. "Red man syndrome" (RMS), which is characterized by erythema, pruritus, and in some cases, hypotension and angioedema (1, 3, 6, 14), has been described secondary to vancomycin administration; but little is known regarding the mechanism for this reaction. Historically, RMS was thought to be related to the concentration of the vancomycin solution and the rate of intravenous administration (4, 8, 12, 13). Typically, the reaction is not seen beyond the first dose (1, 3, 6, 14). Studies with healthy volunteers have shown a relationship between the release of histamine and the amount of histamine in plasma secondary to vancomycin administration and the severity of the reaction (8, 15, 18, 20). Overall, the exact incidence of the reaction in patients is not known, but it has been suggested that it is probably underreported (14). Another hypothesis suggests that the histamine stores in infected patients may have already been depleted in response to infection or trauma, and therefore, the patients would elicit a blunted or absent response when they are challenged with vancomycin (14). Teicoplanin, a glycopeptide antibiotic with a spectrum of activity similar to that of vancomycin, does not elicit RMS in volunteers at a dose of 15 mg/kg of body weight (19). However, information regarding teicoplanin and this reaction in patients has not been studied prospectively.

The purpose of this investigation was to examine the effect of teicoplanin and vancomycin on histamine release and associated clinical reactions in patients being treated for gram-positive infections and to compare the histamine release with that in healthy volunteer subjects (HVS) receiving vancomycin.

MATERIALS AND METHODS

This study was approved by the Wayne State University Human Investigation Committee. Informed consent was obtained from all participants prior to enrollment in the study. Patients enrolled in a trial on the clinical efficacy of teicoplanin and vancomycin for bacteremia or endocarditis at Detroit Receiving Hospital were eligible for inclusion in the histamine evaluation. Exclusion criteria consisted of history of drug allergy, atopy, and consumption of antihistamine-containing products and/or vancomycin administration within 7 days of the study.

Teicoplanin (400 mg; lot IC-4292) and vancomycin (lot 4PL19A) were supplied as lyophilized powders by Merrell Dow Research Institute and Eli Lilly & Co., respectively, and were reconstituted with sterile water and then diluted in 250 ml of 0.9% normal saline. Teicoplanin (30 mg/kg of body

* Corresponding author.

TABLE 1. Demographics of patients and HVS examined in this study

Treatment	No. of subjects	Gender[a]	Race[b]	No. of subjects with bacteremia[a]	Age (yr)[c]	Wt (kg)[c]	CL_{CR} (ml/min)[c,d]
Teicoplanin (30 mg/kg)	10	6 M, 4 F	3 W, 7 B	5	34.6 ± 6.2	65.1 ± 12.0	75.6 ± 32.6
Vancomycin (1,000 mg)	15	12 M, 3 F	5 W, 9 B, 1 H	7	34.5 ± 7.9	72.7 ± 14.0	95.3 ± 30.0
Placebo or vancomycin (1,000 mg)	10	7 M, 3 F	10 W	0	30.5 ± 3.1	77.3 ± 20.5	93.2 ± 21.4

[a] M, male, F, female.
[b] W, white; B, black; H, Hispanic.
[c] Values are means ± standard deviations.
[d] CL_{CR}, creatinine clearance estimated by the method of Cockcroft and Gault (2).

weight) and vancomycin (1,000 mg) were infused over 60 min via an electronic infusion device through a central or peripheral venous catheter.

Ten HVS were included as a RMS-positive control group. Volunteers were randomized in a double-blind crossover design to receive either intravenous vancomycin or placebo (saline), with a minimum 1-week washout period between treatments. Drug administration was carried out as described above. Exclusion criteria for HVS consisted of a history of drug allergy (i.e., atopy) or abnormal physical examination or baseline laboratory studies. All HVS were admitted to a patient unit at the Detroit Receiving Hospital for drug administration and clinical evaluation. HVS were asked to refrain from taking antihistamine products on the day of and 24 h prior to the study days. Creatinine clearance was estimated by the method of Cockcroft and Gault (2).

Patients were evaluated during the administration of the first dose of antibiotic. A blinded investigator (L.H.W.) assessed patients and HVS for signs and symptoms consistent with RMS defined as pruritus, erythema or flushing of the upper torso, angioedema, or cardiovascular depression (defined as a drop in diastolic pressure of >10 mm Hg) (14). With the subjects in the supine position, blood pressure was obtained every 10 min during the infusion. Because pruritus is a subjective complaint, we attempted to avoid the introduction of bias by observing the patient or subject for behavioral changes consistent with pruritus, such as scratching. Patients or HVS were not prompted by the investigator to register complaints, and only those complaints volunteered by the patient or subject were recorded. If erythema became apparent to the investigator, the patient or subject was asked for confirmation of a color change after self-examination with a mirror. Erythema was regarded as a color change verified by both the patient or subject and the investigator. Angioedema was diagnosed by the investigator if there was evidence of subcutaneous swelling or if the patient complained of swelling which limited motion. The presence of one of the three signs and symptoms described above was considered to be a mild reaction, the presence of two was considered to be a moderate reaction, and the presence of three was considered to be a severe reaction. Each patient was monitored for infusion-related symptoms during and for 1 h after drug administration.

Plasma histamine concentrations were determined for all patients and HVS just prior to drug administration (baseline); at 30 min into the infusion (midpoint of infusion); and at 0, 0.5, and 1 h postinfusion. Each sample was obtained by drawing 4 ml of blood into a prechilled glass vacuum tube containing EDTA; the tube was then immediately placed on ice. Cells were separated by refrigerated centrifugation and were stored at −20°C until they were assayed. Plasma histamine concentrations were determined by radioimmunoassay (^{125}I Histamine RIA Kit Prod. 1302, AMAC) by using previously described procedures (10). Five plasma standards were used to generate a standard curve (0.05 to 5 ng/ml). Samples found to have concentrations greater than 5.0 ng/ml were diluted to bring the result back into the concentration range for the standard curve. The sensitivity of the assay was 0.02 ng/ml. The between-day coefficients of variation for the 0.5-, 1.5-, and 5-ng/ml histamine control standards were 13, 18.1, and 16%, respectively. To determine the magnitude of histamine release during and after antibiotic treatment, the area under the histamine concentration-time curve (AUC) was calculated by using the linear trapezoidal rule (7).

Blood for determination of antibiotic concentrations in serum was obtained at 0, 30, and 60 min after the end of the infusion. Vancomycin and teicoplanin concentrations in serum were determined by fluorescence polarization immunoassay (Abbott Laboratories, Chicago Ill., and International BioClinical, Portland, Oreg.). The lower limit of detection was 0.6 μg/ml for vancomycin and 0.5 μg/ml for teicoplanin. We have previously reported coefficients of variation for control samples (7, 35, 75 μg/ml) that were run with each group of subject specimens; they averaged <6% for vancomycin and <13% for teicoplanin (16, 17).

Statistical analysis. Discrete data were analyzed by Fisher's exact test. Demographic data and the effect of drug on histamine release, histamine AUC, and blood pressure between treatment groups were compared by analysis of variance with Tukey's test for multiple comparisons. Peak concentrations of vancomycin in HVS and patient serum were analyzed by an unpaired *t* test. The relationships between maximum plasma histamine concentration, plasma histamine AUC, and severity of RMS and the relationship of dose (milligrams per kilogram) and histamine AUC were compared by using Spearman's rank correlation. A *P* value of <0.05 was considered significant in all instances.

RESULTS

Twenty-five patients with a history of intravenous drug use who were being treated for suspected gram-positive infections were enrolled in the study. Fifteen patients (12 males, 3 females) received vancomycin and 10 patients (6 males, 4 females) received teicoplanin. Ten HVS (seven males, three females) were enrolled into the study as positive controls. Demographic data for patients and HVS are listed in Table 1. With regard to demographic data, HVS were significantly younger and heavier than were the patients who received vancomycin or teicoplanin. Estimated creatinine clearance was not different between patients who received

TABLE 2. Results of clinical evaluation[a]

Treatment	No. of subjects	Histamine concn (ng/ml) (change from baseline concn [ng/ml])	Histamine AUC (ng · h/ml)	Dose (mg/kg)	Antibiotic peak concn	Oral temp (°F [°C])	Change in diastolic blood pressure (mm Hg)	Subjective evaluation (no. of subjects)[b]		
								P	E	A
Teicoplanin	10	0.43 ± 0.27 (+0.34 ± 0.51)	0.84 ± 0.50	30	153.8 ± 34.3	102.4 ± 1.2 (39.1 ± 0.9)	−4.4 ± 6.1	0	0	0
Vancomycin	15	0.42 ± 0.41 (+0.17 ± 0.42)	1.2 ± 1.2	14.3 ± 2.8	40.8 ± 13.0	102.3 ± 1.3 (39.1 ± 0.8)	−4.13 ± 6.8	0	0	0
Volunteers	10									
Placebo		0.51 ± 0.52 (+0.18 ± 0.34)	1.03 ± 1.02	NA[c]	NA	98.3 ± 0.4 (36.8 ± 0.4)	−5.2 ± 5.7	0	0	0
Vancomycin		0.51 ± 0.45 (+1.30 ± 2.57)	1.71 ± 1.71	13.9 ± 3.8	49.9 ± 5.8	97.9 ± 0.7 (36.6 ± 0.3)	−14.3 ± 7.08	9[d]	9[d]	3[d]

[a] Values are means ± standard deviations.
[b] P, pruritus; E, erythema; A, angioedema.
[c] NA, not available.
[d] Statistically significant difference ($P < 0.001$).

vancomycin and HVS, but patients who received teicoplanin had significantly lower creatinine clearances than did patients who received vancomycin or HVS. All patients were febrile prior to (within 12 h) or at the time of receipt of the first dose of either vancomycin or teicoplanin. Seven patients who received vancomycin and five patients who received teicoplanin were bacteremic. There were no differences in peak vancomycin concentrations in patients compared with those in HVS.

Although baseline histamine concentrations were variable within groups, there was no statistical difference in baseline histamine concentrations for all groups. Histamine elevations (>1-ng/ml change from baseline) were noted in one patient who received vancomycin, one patient who received teicoplanin, two HVS who received vancomycin, and no HVS who received saline (Table 2). The histamine AUC between groups was not statistically different.

There were no clinical manifestations consistent with RMS seen in any patient. However, 9 of 10 (90%) HVS had clinical symptoms, ranging from mild to severe (one patient with mild symptoms, 5 patients with moderate symptoms, 3 patients with severe symptoms), that were consistent with RMS. The most predominant reaction was erythema and pruritus. The average time for a reaction to occur from the start of the infusion was 32 ± 17.5 min. Most reactions abated within 1 h (67.9 ± 21.7 min; range, 40 to 113 min) after the end of infusion. Of interest, 2 of 15 patients who received vancomycin, 3 of 10 patients who received teicoplanin, 7 of 10 HVS who received vancomycin, and 3 of 10 HVS who received saline had a decrease in diastolic pressure of ≥10 mm Hg (ranges, 2 to 25, 2 to 14, 3 to 30, and 12 to 13 mm Hg, respectively). There was no relationship between the maximum plasma histamine concentration or histamine AUC and the severity of RMS in HVS. In addition, there was no relationship between histamine AUC and dose (milligrams per kilogram) for patients who received vancomycin or teicoplanin. Interestingly, elevation of the plasma histamine concentration from the baseline was greatest (increase of 9.3 ng/ml) in a volunteer with the severest symptoms (erythema, pruritis, angioedema, and blood pressure drop of 25 mm Hg).

DISCUSSION

Our data appear to confirm that the incidence of RMS secondary to vancomycin or teicoplanin treatment in patients is low. Similar to previous investigations (8, 15, 18–20), ≈90% of HVS experienced RMS, with pruritus and erythema being the most common symptoms. The reason for the disparity in the occurrence of RMS between patients and HVS is unknown. However, it has been suggested that the incidence in patients may be underreported (14). In a recent investigation, Wallace et al. (21) prospectively observed 33 patients who received 1 g of vancomycin over a 60-min infusion period for the occurrence of RMS. Patients were randomized to receive either diphenhydramine or placebo prior to their first dose of vancomycin. The incidence of RMS was reported to be 47% in 17 patients who received vancomycin alone. RMS did not occur in 16 patients who were pretreated with diphenhydramine. It should be noted that seven of eight of the patients who exhibited RMS had a history of penicillin allergy, although we are unaware of any relationship between penicillin allergy and RMS. There were several patients in the study by Wallace who received vancomycin as prophylaxis, but the majority of patients received vancomycin for the treatment of infection. Previous investigations in HVS have determined that there is a relationship between the dose of vancomycin administered and the incidence of RMS. Healy et al. (8) reported that RMS occurred in 9 of 11 HVS who received 1 g of vancomycin over 60 min but not in subjects who received 500 mg over 1 h. In our study, we used a fixed dose of 1,000 mg infused over 1 h. The range in our patient and HVS population was wide (for patients, the mean was 14.3 ± 2.8 mg/kg and the range was 9.2 to 22 mg/kg; for HVS, the mean was 13.9 ± 3.8 and the range was 8.9 to 21.5 mg/kg). However, we found no relationship between the dose and the incidence of RMS.

It has also been shown that there is a relationship between the amount of histamine released and the severity of reaction (15). Another investigation of HVS (18) reported findings similar to those of Wallace et al. (21). RMS secondary to vancomycin was effectively blocked by premedicating HVS with the antihistamine hydroxyzine, further implicating histamine as the primary cause of the reaction (18). In the present study, RMS was not found secondary to vancomycin administration in patients; plasma histamine concentrations were variable in all groups; and there was no relationship between plasma histamine concentration, histamine AUC, and the severity of RMS in HVS.

Teicoplanin, a glycopeptide similar to vancomycin, has not been shown to elicit histamine release in plasma or RMS in HVS at a dose of 15 mg/kg (19). We examined the effects

of high-dose teicoplanin (30 mg/kg) in patients and found no difference in plasma histamine concentrations compared with those in patients who received vancomycin and no cases of RMS or other subjective complaints secondary to the infusion of teicoplanin. These data are similar to those found in multicenter clinical trials that compared the efficacy of teicoplanin (238 patients) with that of vancomycin (239 patients). While vancomycin was administered over a 60-min infusion period at the recommended dosage of 15 mg/kg every 12 h, dosages for teicoplanin throughout the studies described here ranged from 6 to 30 mg/kg/day, with infusion rates being as short as 30 min. The incidence of symptoms compatible with RMS for both glycopeptides are reported to be low (1 of 128 subjects who received teicoplanin and 1 of 239 subjects who received vancomycin [both 0.42%]). In the one case of RMS secondary to vancomycin administration, the patient was switched to teicoplanin without further problems (9). There is a recent case report of RMS secondary to teicoplanin administration (5). A 59-year-old male patient with a history of chronic obstructive pulmonary disease received teicoplanin at a dose of 8 mg/kg (400 mg) intravenously over a 3-min infusion period. The patient developed a nonpruritic generalized erythema, asthma, and dyspnea. All signs and symptoms resolved within 15 min of the injection. There was no information regarding other medications the patient may have been receiving at the time of the reaction. In addition, the signs and symptoms reported are not consistent with classic RMS (14), and we argue that this case represents an allergic reaction to teicoplanin and not RMS. From our data, it appears that the histamine response to administration of glycopeptides such as vancomycin and teicoplanin is highly variable in both patients and HVS. This is consistent with the observations made by other investigators (18) that histamine release secondary to glycopeptide administration between subjects is dissimilar and that the determinants of release are a unique property of individual patients.

The fact that RMS was observed only in HVS supports the clinical observations that RMS secondary to glycopeptides in our patient population was low. However, because we could find no relationship between plasma histamine concentration or AUC with severity of RMS in HVS suggests that the syndrome known as RMS may be more complicated than the simple relationship of histamine in plasma and the rate or severity of reaction. As stated above, the reason for the discrepancy between RMS in patients and HVS is unclear, but it is possible that infected patients are less likely to mount a histamine-mediated RMS response to glycopeptides. All of our patients were febrile, and approximately 50% were bacteremic at the time of entry into our study. It has been suggested that febrile or septic patients may not react to histamine releasing agents like vancomycin if their histamine stores have already been depleted in response to trauma or infection (14). In addition, if histamine is the major cause of RMS, it is possible that either receptor sites for histamine are altered or an unknown nonallergenic substance which competes with histamine for the receptor site is released during infectious states. All of our patients had a history of intravenous drug use, and many patients had recently injected narcotics. Narcotics have been demonstrated to cause histamine release in animals and humans (11). It is possible that frequent or chronic use of intravenous narcotics may lead to desensitization or a blunted histamine response and that this may account for the absence of RMS in this patient population. Poor venous access and the urgent need to begin antibiotics limited our ability to obtain multiple blood samples (more than four) for the quantitation of histamine; however, it is unlikely that we missed a rise in histamine concentrations on the basis of results of previous investigations (15, 18–20). Further research in patients and HVS is warranted to understand the physiologic differences and to better characterize the mechanism of RMS.

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