

Vancomycin hypersensitivity: Synergism with narcotics and "desensitization" by a rapid continuous intravenous protocol

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Background: We examined the clinical spectrum of patients with persistent adverse reactions to vancomycin, assessed contributing factors, and evaluated the efficacy and safety of a rapid continuous intravenous "desensitization" protocol in these patients.

Methods: Seven patients with serious staphylococcal infections resistant to β -lactam antibiotics whose adverse reactions to vancomycin persisted despite slowing of the vancomycin infusion and pretreatment with H_1 -antihistamine were studied. All seven patients underwent a rapid continuous intravenous desensitization protocol with multiple small increases in vancomycin concentration tightly regulated with a syringe pump.

Results: Most of the seven patients safely achieved, during the first day, a vancomycin infusion rate (VIR) sufficient, or close to sufficient, to provide the desired vancomycin dose. In three patients there appeared to be a threshold VIR beyond which adverse reactions were repeatedly elicited; these reactions abated when the VIR was slightly lowered. Narcotic administration was found to adversely affect treatment with vancomycin. After concurrent narcotic administration was discontinued in three patients, they and the other four patients successfully completed the full course of treatment with vancomycin.

Conclusion: Patients whose adverse reactions to vancomycin did not respond to slowing of the infusion rate and additional H_1 -antihistamines can be safely treated with a rapid continuous intravenous desensitization protocol and discontinuance of narcotic administration. (*J ALLERGY CLIN IMMUNOL* 1994;94:189-94.)

Key words: Vancomycin, hypersensitivity, desensitization, threshold, narcotic

Vancomycin is a complex tricyclic glycopeptide antibiotic obtained from the norcardia species *Amycolatopsis orientalis*. It has strong bactericidal activity against a broad spectrum of gram-positive bacteria. Its major antibacterial mechanism appears to be the inhibition of bacterial cell wall synthesis by interference with the incorporation of the lipid-phosphodisaccharide-pentapeptide complex, a step earlier than the reactions inhibited by β -lactam antibiotics.¹ Vancomycin also alters bacterial cell membrane permeability and inhibits RNA synthesis.¹ Because of low cross resistance with β -lactam antibiotics, vancomycin is highly effective in the treatment of methicillin-resistant (β -

Abbreviations used

MRSA: Methicillin-resistant *Staphylococcus aureus*
VIR: Vancomycin infusion rate

lactam resistant) *Staphylococcus aureus* (MRSA) and *S. epidermidis* infections.¹⁻³ It is also widely used to treat gram-positive infections in patients who have β -lactam antibiotic hypersensitivity or whose infections fail to respond to β -lactam antibiotics.¹ Because of its long half-life in patients with kidney failure, vancomycin is frequently given as a single dose to treat gram-positive infections in these patients.¹ In orally administered form, vancomycin is used in the treatment of pseudomembranous colitis.

A broad spectrum of adverse reactions has been reported to complicate vancomycin administration. Adverse reactions include local phlebitis; nephrotoxicity; otic toxicity; hematopoietic changes including leukocytosis, eosinophilia, neu-

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TABLE I. Indications for further vancomycin administration in seven patients who had significant adverse reactions to vancomycin despite slowing of infusion and H₁ antihistamine administration

- Meningitis associated with epidural catheter leakage—unresponsive to β -lactam and aminoglycoside antibiotics
- MRSA—osteomyelitis of a bone graft
- MRSA—osteomyelitis of tibia
- β -Lactam-resistant *S. epidermidis* infection of a decubitus ulcer
- AICD implantation for treatment of sudden cardiac arrest secondary to recurrent ventricular tachycardia; recent MRSA infection of abdominal abscess and urinary tract; positive MRSA culture from nasal passage
- β -Lactam resistant *S. epidermidis* osteomyelitis and nonhealing ulcer
- Chronic sinusitis with MRSA despite multiple sinus procedures, including surgery, lavage, and mucus extraction

AICD, Automatic internal cardiac defibrillator.

TABLE II. Spectrum of adverse reactions to vancomycin in seven patients

Reaction	Patients	
	No.	%
Pruritus, intense	7	100
Flushing/erythema	5	71
Urticaria	5	71
Hypotension	2	29
Anxiety	2	29
Dyspnea	1	14
Throat tightness	1	14
Maculopapular rash	1	14

tropenia, agranulocytosis, and thrombocytopenia; dermatologic manifestations including maculopapular, urticarial, and exfoliative dermatitis; and fever^{1, 4-10} The most common adverse reaction is the "red man syndrome," which is defined as a constellation of signs and symptoms that include flushing, pruritus, and less commonly, hypotension and chest discomfort.¹¹⁻¹⁵ The red man syndrome occurred in 35% to 90% of normal volunteers infused with 1 gm of vancomycin over 1 hour.^{12, 15-17} Although the majority of the reactions were mild, some were severe. The severity correlated with the amount of histamine released into the plasma, suggesting that the reactions were caused by mast cell and/or basophil mediator release.^{12, 15} The development of the red man syndrome is usually related to the rate of vancomycin infusion; the reaction abates with slowing of the vancomycin infusion rate (VIR) in the majority of patients. In one study none of the volunteers who exhibited the red man syndrome at a VIR of 1000 mg/hr had the reaction when the VIR was reduced to 500 mg/hr.¹² Pretreatment with H₁ antihistamines frequently ameliorates the severity of the reactions.^{15, 17}

During the past 3 years, we encountered patients whose adverse reactions to vancomycin persisted despite marked slowing of the VIR and the addition of H₁ antihistamines. Because the patients continued to require vancomycin, all underwent a rapid continuous intravenous "desensitization" procedure and eventually completed their course(s) of vancomycin treatment. In some of these patients there appeared to be a threshold infusion rate beyond which adverse reactions were repeatedly elicited. In the majority of the patients, concomitant treatment with narcotics was found to complicate treatment with vancomycin.

METHODS

Patients

We were consulted on seven patients who had marked adverse reactions to treatment with vancomycin despite slowing of the infusion rate and the addition of H₁ antihistamines in six of the seven patients. They ranged in age from 2½ to 61 years, and four of the patients were female. One patient had the adverse reactions during the first dose of the first course of vancomycin. Two patients had received vancomycin infusions without difficulty for 2 or more weeks but thereafter had progressive adverse reactions. At least one of the other four patients had tolerated previous courses of vancomycin. Consultants from the Infectious Disease Unit recommended continued treatment with vancomycin. Indications for further administration of vancomycin are listed in Table I. In six patients infection by a *Staphylococcus* species resistant to β -lactam antibiotics was involved. The other patient had meningitis, associated with a leaking epidural catheter. The infection had not responded to treatment with broad-spectrum β -lactam and aminoglycoside antibiotics, raising the possibility that the infection might be caused by *S. epidermidis*. The spectrum of reactions is listed in Table II. All seven patients experienced intense pruritus. The majority also experienced flushing or erythema and/or urticaria. Two of the seven patients had hy-

TABLE III. Vancomycin rapid intravenous desensitization protocol

Time (hr:min)	Vancomycin concentration (mg/ml)	Fluid infusion rate (ml/min)	VIR (mg/min)	Cumulative dose (mg)
0:00	0.0001*	1.0	0.00010	0
0:10	0.001	0.33	0.00033	0.0010
0:20	0.001†	1.0	0.0010	0.0043
0:30	0.01	0.33	0.0033	0.0143
0:40	0.01	1.0	0.010	0.047
0:50	0.1	0.33	0.033	0.147
1:00	0.1	1.0	0.10	0.48
1:10	1.0	0.33	0.33	1.48
1:20	1.0	1.0	1.0	4.78
1:30	10.0‡	0.22‡	2.2	14.8
1:40	10.0‡	0.44‡	4.4	37

The Bard syringe pump was used as the delivery system. Pretreatment and concurrent treatment consisted of H₁ antihistamines (e.g., hydroxyzine, astemizole, doxepin, diphenhydramine).

*Typical starting concentration in patients with severe systemic reactions to previous vancomycin infusions.

†Typical starting concentration in patients with moderate reactions to previous vancomycin infusions.

‡Vancomycin may be diluted to produce a less concentrated solution such as 2.0 to 5.0 mg/ml. The fluid infusion rate should then be raised to maintain the same VIR. A standard infusion pump can be used to deliver the remainder of the vancomycin dose.

potension. In one patient dyspnea and a sensation of throat tightness developed.

Protocol

We developed a rapid continuous intravenous "desensitization" protocol, which is outlined in Table III. All patients were pretreated with H₁ antihistamines; the first patient also received an H₂ antihistamine. The infusion rates were tightly regulated with a Bard syringe pump (C.R. Bard, N. Reading, Mass.). An appropriate starting vancomycin concentration and infusion rate were chosen on the basis of the severity of a patient's previous reaction: initial VIR of 0.0001 mg/min was chosen for patients with severe systemic reactions and a 10-fold higher initial VIR was chosen for patients with moderate reactions to previous vancomycin infusions. The VIR was raised 3- to 3.3-fold every 10 minutes, resulting in a 10-fold increase every 20 minutes. For patients who had an adverse reaction at a given VIR, the VIR was decreased 3- to 10-fold (except as noted below) before the schedule was resumed. After a VIR of 2.2 to 4.4 mg/min was achieved, the VIR was kept constant for delivery of the remainder of the vancomycin dose. Subsequent doses were initiated at this VIR, except as noted below. Patients in whom a VIR of 2.2 to 4.4 mg/min could not be achieved continued to receive vancomycin at the highest tolerated infusion rate for the first day, and the rate was gradually advanced over the next few days as tolerated.

RESULTS

Clinical course

Case A. A 2½-year-old boy with a history of cerebral palsy, seizure disorder, gastroesophageal reflux, and recurrent otitis media was admitted for funduplication, myringotomy, and ear tube place-

ment. Despite perioperative administration of cefotetan, meningitis associated with a leaking epidural catheter developed postoperatively. The catheter was inserted for perioperative pain control. The catheter was removed, and the patient was switched to morphine for pain management. Administration of cefotaxime and gentamicin was started. Vancomycin was added to cover the possibility that the infection was caused by *S. epidermidis*. After the patient received 50 mg of vancomycin, delivered over 20 minutes, marked flushing of the head and neck, pruritus, and hypotension (78/30 mm Hg) developed. The next day, a 1 mg test dose of vancomycin was infused over 15 minutes. The patient again experienced flushing and pruritus. Because the patient continued to have high fever and pleocytosis, further treatment with vancomycin was deemed to be indicated. The continuous intravenous desensitization protocol was initiated after pretreatment with hydroxyzine and cimetidine. The infusion was started at 0.0001 mg/min. When the infusion rate was advanced to 0.02 mg/min, the patient experienced mild flushing. The VIR was decreased fourfold. The flushing subsided, and incremental advancements were resumed. At 0.1 mg/min, flushing and pruritus returned. The VIR was decreased twofold. The flushing and pruritus once more subsided. The VIR was gradually raised to 0.8 mg/min, and the remainder of the 145 mg dose was successfully infused. Because of the patient's marked sensitivity and uncertainty over whether the desensitized state would be maintained, we initiated the next dose 3 hours later at a VIR of 0.02 mg/min. Flush-

ing and pruritus rapidly developed, necessitating the discontinuation of the vancomycin infusion. Despite the addition of imipenem and rifampin, the patient continued to have high fever and pleocytosis for the next 2 days. Vancomycin was again deemed to be essential. Because narcotics and vancomycin are each independently capable of directly degranulating the mast cells,^{12, 15, 18, 19} we were concerned that they might synergize in causing release of mediators from mast cells in this patient. Hence, the administration of morphine was discontinued and a repeat desensitization to vancomycin was successfully performed according to the protocol. The final rate was modified so that the vancomycin could be infused continuously. Six days later, the infusion was changed so that the patient received 60% of the dose as a pulse over 2 hours four times a day, and the remaining 40% as a continuous infusion. The patient successfully completed his antibiotic course and recovered.

Case B. The patient is a 69-year-old woman with chronic pansinusitis who had undergone endoscopic and open sinus surgeries during the preceding year. She continued to have pansinusitis with symptoms of sinus pressure, purulent rhinorrhea, and cough. Mucus plugs, which were removed endoscopically, and drainage from her maxillary sinuses repeatedly yielded MRSA. She was started on her first course of intravenously administered vancomycin at home and tolerated the treatment for 3½ weeks. The patient then experienced intense pruritus and developed a muculopapular rash associated with the vancomycin infusions. These reactions continued despite marked slowing of the VIR and pretreatment with hydroxyzine. The patient was admitted to the hospital, and the continuous intravenous desensitization protocol was initiated after pretreatment with doxepin. Doxepin was selected because of its strong H₁ antihistamine properties and because the treatment with hydroxyzine had failed. The vancomycin infusion was started at a rate of 0.001 mg/min. The patient tolerated the desensitization procedure uneventfully until infusion at a rate of 4.4 mg/min was started; thereafter, generalized pruritus developed. The VIR was decreased and readvanced to 2.2 mg/min. The remainder of the 400 mg dose and subsequent doses that day were infused at a rate of 2.2 mg/min without difficulty. On the following day, the VIR was advanced uneventfully to 3.3 mg/min. On the next day, on advancement of the VIR to 4.4 mg/min, generalized pruritus again developed. Pruritus ceased when the VIR was lowered to 3.3 mg/min. The patient completed the remainder of her 6-week

course of vancomycin at home. The drug was given in a dose of 400 mg four times a day, administered at a VIR of 2.2 mg/min.

Of the other five patients, three achieved the desired VIR, without incident, over a course of 2 to 2.5 hours on the first day of the desensitization protocol. Two of these three patients completed the entire vancomycin course without difficulty. One of the three patients underwent placement of an automatic internal cardiac defibrillator for treatment of recurrent ventricular tachycardia. She experienced flushing when meperidine was added to her treatment for postoperative pain control. She again tolerated the vancomycin at the desired VIR when the narcotic was discontinued several days later.

The other two patients could not achieve a sufficiently high VIR to receive the desired vancomycin dose, despite multiple attempts to advance the VIR on the first day of treatment. Like the patient described in case B, they each appeared to have a threshold VIR beyond which adverse reactions (intense pruritus, localized flushing, and/or urticaria) were repeatedly elicited, but both tolerated a slightly lower VIR. One of these two patients was receiving a narcotic for pain control. Her threshold could not be raised for days, until the narcotic was discontinued. She then tolerated the desired threefold higher VIR. For the other patient, the threshold was gradually raised fourfold over 5 days, concomitant with an increase in H₁ antihistamine dosage.

DISCUSSION

In three of the seven cases reported in this series, there appeared to be a threshold VIR beyond which adverse reactions were repeatedly elicited; these reactions abated when the VIR was slightly lowered. Though the threshold VIR remained constant throughout the first day in all three patients, the stability on subsequent days varied: one patient remained remarkably stable (case B), one tolerated a dose that was gradually increased over several days, and one was unable to tolerate an increased dose until concurrent narcotic administration was stopped. The existence of a stable threshold, which can be repeatedly traversed in a short period of time to induce adverse reactions, and the rapid subsidence of symptoms on lowering the VIR argues against the reactions being mediated by IgE antibodies to vancomycin in these patients. The observation that at least one other patient had a reaction to vancomycin at the time of first exposure also argues against an IgE-mediated reaction in that patient (case A).

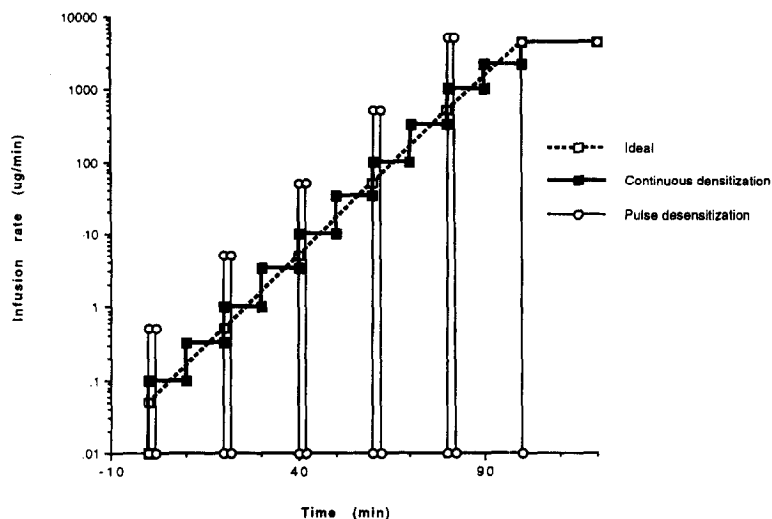


FIG. 1. Comparative infusion rates of the rapid continuous intravenous desensitization protocol (black squares) versus conventional pulse desensitization protocol (open circles). The rapid continuous protocol calls for continuous administration of the drug while making small frequent incremental increases in the drug infusion rate. In contrast, the conventional protocol requires that a bolus of the drug be given over a brief interval, followed by a period of no drug administration, followed by a bolus many times higher in concentration.

Urticaria and maculopapular rash are not generally included in the description of the red man syndrome, but both have been observed in patients experiencing an otherwise typical red man syndrome reaction to vancomycin.²⁰⁻²³ Hence, the spectrum of adverse reactions experienced by the patients in this study is similar to that found in the red man syndrome. It is likely that these patients represent severe variants of the syndrome and that their mast cells and/or basophils may be more readily degranulated by vancomycin.

In five of the seven subjects, narcotics appeared to lower the threshold at which the patient had adverse reactions to the infusion of vancomycin. While receiving morphine, the patient in case A repeatedly had adverse reactions at low VIRs, and the high VIR initially achieved could not be maintained. Similarly, the threshold of a second patient was able to be raised only after the narcotic was discontinued. A third subject, who was tolerating the vancomycin infusion, had adverse reactions when narcotics were added. She again tolerated the infusion when the narcotics were discontinued. Two other patients were receiving narcotics before the desensitization protocol; their adverse reactions were substantially reduced after treatment with narcotics was stopped. The residual reactions, however, were still intolerable to the patients, and hence, they underwent the desensitization procedure.

The adverse interaction between vancomycin

and narcotics, observed in the majority of our patients, strongly suggests that one should search for concurrent narcotic administration in patients whose adverse reactions to vancomycin do not respond to slowing of the infusion rate and pretreatment with H₁ antihistamines. Both vancomycin and narcotics induce a dose- or rate-dependent mast cell degranulation^{12, 15, 18, 19} and likely synergize to produce the adverse reactions. As illustrated by our patients, the synergism is bidirectional: some patients who tolerated vancomycin infusion had adverse reactions when a narcotic was added, and some patients who tolerated treatment with narcotics had adverse reactions when vancomycin infusion was started.

The observed synergism between vancomycin and narcotics suggests that similar interactions may occur with other drugs or treatments that can induce mast cell degranulation, such as radiocontrast materials and muscle relaxants. Interactions may also occur between IgE antibody-mediated hypersensitivity reactions and compounds that induce direct mast cell degranulation. Hence, consideration should be given to limiting the use of narcotics in patients undergoing desensitization with antigens that have elicited IgE-mediated reactions.

The rapid continuous intravenous desensitization protocol involves multiple small increases in the dose of the drug (Fig. 1). In comparison, a conventional protocol, which calls for the same

10-fold increase in dose over 20 minutes, would require the administration of a bolus of the drug over 3 to 5 minutes, followed by an interval of 15 minutes during which no drug is administered. A 10-fold greater dose is then given with the next bolus infusion. The continuous intravenous infusion protocol that we have developed should be safer not only because smaller dose increments are used, but also because the continuous infusion delivers only a small amount of drug during any interval. Furthermore, the infusion can be rapidly discontinued. Because of these advantages, we were able to make relatively rapid advances in dosage safely. In uncomplicated cases the desired infusion rate was achieved in less than 2 hours. This process is considerably faster than the two previously reported protocols of vancomycin desensitization (involving one patient treated with each protocol). Lin²⁴ used a slow desensitization protocol involving a serial 10-fold increase in dose every 24 hours, 4 day were required to achieve the desired infusion rate. Lerner and Dwyer²⁵ also used a serial 10-fold increase in dose and achieved the desired infusion rate over 4 hours. Despite pretreatment with both H₁ antihistamine and corticosteroids, their patient experienced continuous pruritus.²⁵

In summary, patients whose adverse reactions to vancomycin were suggestive of the red man syndrome, but who did not respond to slowing of the infusion rate and addition of H₁ antihistamines, were treated with a rapid continuous intravenous desensitization protocol, combined with discontinuation of narcotics as applicable. The infusion protocol that was developed and the interaction principle that was uncovered are currently being applied to the management of adverse reactions to other agents.

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