Limitations of Vancomycin in the Management of Resistant Staphylococcal Infections

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Vancomycin is effective against methicillin-resistant Staphylococcus aureus and has been widely used in the past few years. However, several recent reports have highlighted the limitations of vancomycin, and its role in the management of serious infections is now being reconsidered. Vancomycin treatment failure rates are associated with an increase in the minimum inhibitory concentration as well as a decrease in the rate of bacterial killing. The intrinsic limitations of vancomycin also include poor tissue penetration, particularly in the lung; relatively slow bacterial killing; and the potential for toxicity. In addition, intermediate-level vancomycin resistance has emerged among staphylococci, as have rare cases of fully resistant strains. Because of these problems, when using vancomycin, it is probably prudent to carefully establish the diagnosis, test for antimicrobial susceptibility, and monitor serum trough concentrations to ensure adequate dosing.

Vancomycin, introduced over 50 years ago, retains clinical utility. However, it is associated with several limitations, including relatively slow bactericidal activity, fluctuating MICs, the development of resistance and associated therapeutic failure, poor pharmacokinetic properties, and the potential for serious toxicity [1]. This article will discuss these limitations, along with the current role of vancomycin in the management of infections due to resistant strains of Staphylococcus aureus, specifically methicillin-resistant S. aureus (MRSA).

CLINICAL RESPONSE TO VANCOMYCIN

Vancomycin failure rates among patients with endocarditis, bacteremia, or bacteremic pneumonia due to methicillin-susceptible Staphylococcus aureus (MSSA) or MRSA have been published since 1977, and they have ranged from 37%, as noted in the first published report, to as high as 50% [2]. Nafcillin was used as a comparator in several of studies of vancomycin failure. In 1990, Small and Chambers [3] found a vancomycin failure rate of 38% in a series of 13 patients with endocarditis due to MSSA, and they contrasted this finding with a reported failure rate of only 1.4% with nafcillin. In a 1997 study of MSSA endocarditis, failure rates of 50% with vancomycin and 26% with nafcillin were reported [4]. A 2003 study of bacteremia also showed a higher failure rate with vancomycin than with nafcillin (20% vs. 4%, respectively) [5]. Moreover, therapy with vancomycin (vs. nafcillin) was significantly associated with relapse.

Two studies have evaluated the performance of vancomycin in patients with staphylococcal bacteremic pneumonia [6, 7]. In the first study, Gonzalez et al. [6] prospectively studied all patients at their institution who had bacteremic pneumonia due to S. aureus during an outbreak of MRSA infections, comparing the outcomes of infections due to MRSA (n = 32) with those of infections due to MSSA (n = 54). Although the mortality and complication rates were not statistically significantly different for patients with MRSA infections versus those with MSSA infections, the mortality rate was significantly higher among patients with MSSA infections who received vancomycin than among those who received cloxacillin (41% vs. 0%; P < .01). Furthermore, multivariate analysis of all cases showed a correlation between mortality and vancomycin treat-
ment (odds ratio [OR], 14), whereas mortality was even higher when vancomycin treatment was used in patients with respiratory distress (OR, 38.46) [6]. In the second study [7], which included 60 patients with confirmed nosocomial bacteremic pneumonia due to staphylococcal infection, 70% of infections were due to methicillin-resistant strains. The rate of infection-related deaths was high (~40%) and was greater among patients who received empirical treatment with vancomycin than among those who received empirical treatment with a β-lactam (50% vs. 28% for patients with MSSA infections; 46% vs. 25% for patients with MRSA infections); however, this difference did not achieve statistical significance [7]. The authors noted that their findings might have been partially explained by the fact that patients receiving β-lactam agents were younger and had lower Acute Physiology and Chronic Health Evaluation II scores, but they also suggested that the relatively slow activity of vancomycin may have been associated with a higher rate of treatment failure.

These findings suggest that vancomycin failure rates may be even higher as the proportion of resistant isolates increases. Decreasing vancomycin bactericidal activity and fluctuating MICs compound the problem in invasive S. aureus infections [8]. In addition, an in vitro study evaluating the effect of several antibiotics (vancomycin, nafcillin, clindamycin, and linezolid) showed that antibiotics have differing effects on the expression of toxins by staphylococci [9]. Both MSSA and MRSA strains showed that antibiotics have differing effects on the expression of toxins (by suppressing translation but not transcription), nafcillin stimulated toxin production, and the toxin levels associated with vancomycin were comparable to those noted in control samples not exposed to antibiotics [9].

**FACTORS AFFECTING THE RESPONSE TO VANCOMYCIN**

**In vitro susceptibility.** Susceptibility noted among isolates during in vitro testing does not always predict clinical response; however, higher MICs are correlated with a greater likelihood of treatment failure [2, 10]. Moise-Broder et al. [10] studied 102 MRSA isolates recovered from vancomycin-treated patients and evaluated the relationship between the MIC and clinical failure rates. As shown in figure 1, these researchers found a linear relationship between the MIC and clinical failure rates [10]. Similarly, Stryjewski et al. [11] reported that vancomycin, when used as the principal therapy, was significantly associated with treatment failure at 12 weeks in a prospective study of 123 patients with MSSA bacteremia who were receiving hemodialysis (31% vs. 13% of patients receiving the comparator cefazolin; P = .02). In 2006, the Clinical and Laboratory Standards Institute lowered the vancomycin susceptibility breakpoint for S. aureus from 4 µg/mL to 2 µg/mL [12]. Hidayat et al. [13] evaluated the treatment outcomes for MRSA infections in association with the serum trough concentrations and the MIC, thus linking the MIC to the clinical response. They found an initial clinical response rate of 74% if the target trough concentration was achieved, regardless of the MIC. Nevertheless, it was reported that, in spite of target trough concentrations having been achieved, patients with infections due to strains with higher MICs (≥2 µg/mL) had lower end-of-treatment response rates (62%, vs. 85% for patients infected with strains with low MICs; P = .02) and a trend toward worse mortality rates (24%, vs. 0% for patients infected with strains with low MICs; P = .16). In a multivariate analysis, a high MIC was also an independent predictor of poor response (P = .03). On the basis of their data, these authors recommend that vancomycin dosing should be adjusted to achieve serum trough concentrations >15 µg/mL [13].

**Bacterial killing.** As described above, the rate of bacterial clearance is lower with vancomycin than with nafcillin, resulting in longer durations of infection. Sakoulas et al. [14] correlated MICs, bactericidal activity, and clinical response. Statistically significant associations were found between treatment failure and both higher vancomycin MICs (P = .02) and reduced killing rates in vitro (i.e., a reduction in log_{10} colony-forming units/mL over 72 h of incubation; P = .03) [14]. As indicated in figure 2, the clinical success rates were higher among patients with MRSA infections in which the bacteria were effectively killed by 72 h; there was 0% clinical success in strains that were killed at a rate of <4.71 log_{10} cfu/mL (n = 9), 23% clinical success in strains that were killed at a rate of ≥4.71–6.26 log_{10} cfu/mL (n = 13), and 50% clinical success in strains that were killed at a rate of ≥6.27 log_{10} cfu/mL (n = 8) [14]. These data suggest that bactericidal activity is an important clinical consideration, at least in infective endocarditis.
Induced heteroresistance in MRSA. MRSA isolates with heterogeneous intermediate resistance to vancomycin are associated with increased rates of treatment failure, prolonged infection, high bacterial loads, and low serum trough concentrations of vancomycin ($P = .006$ for all, compared with vancomycin-susceptible MRSA in patients with bacteremia) [15]. The mechanism of heteroresistance in MRSA is currently not well understood, because the phenotype tends to be unstable without selective pressure from a glycopeptide and is thus difficult to study [16]. It is thought that a dysfunctional accessory gene regulator (agr) operon may confer a survival advantage in the presence of vancomycin, along with enhancement of biofilm formation and physiologic changes that support colonization [17].

PHARMACOKINETICS AND PHARMACODYNAMICS OF VANCOMYCIN

Vancomycin has a complex and variable tissue distribution, its killing activity is time but not concentration dependent, and the relationship between serum concentrations of vancomycin is not well established [18]. However, it is thought that the therapeutic range should include peak concentrations of 30–40 µg/mL, with a trough concentration of $>15$ µg/mL [13, 18].

Tissue penetration. Vancomycin penetrates most tissues, but at variable concentrations, particularly in the lung [18]. In a study of lung tissue specimens recovered from 30 patients undergoing partial lobectomy, Cruciani et al. [19] found that the mean vancomycin concentration after intravenous administration of 1 g via 1-h infusion was 9.6 mg/kg at 1 h but that, by 2 h, it had decreased to 5.5 mg/kg; by 4 h, concentrations of vancomycin were too low to achieve the MIC of 4 µg/mL (the new Clinical and Laboratory Standards Institute breakpoint is 2 µg/mL) and were undetectable in some patients. Lamer et al. [20] evaluated penetration of vancomycin into the epithelial lining fluid from the lower respiratory tract in 14 patients receiving ventilation. There was a significant correlation between plasma and epithelial lining fluid levels of vancomycin, with a ratio of blood to epithelial lining fluid of 6:1. These researchers also assessed the relationship between vancomycin and lung inflammation (as indicated by albumin concentrations $\geq 3.4$ mg/mL) and found that vancomycin penetration was higher in patients with inflammation, suggesting that the concentration is dependent on capillary membrane permeability [20].

Inoculum size. High inoculum sizes have a negative effect on vancomycin efficacy. In an in vitro pharmacodynamic model designed to evaluate the impact of MRSA and MSSA inoculum size on the activities of a variety of antibiotics (vancomycin, nafcillin, linezolid, and daptomycin), LaPlante and Rybak [21] found that high inocula ($9.5$ log$_{10}$ cfu/g) significantly reduced the killing rates of vancomycin and nafcillin. Vancomycin demonstrated bactericidal activity as early as 32 h after administration for low inocula but did not achieve bactericidal activity throughout the 72 h of study for high-inoculum MRSA. The effectiveness of daptomycin was only minimally affected, and that of linezolid was not changed [21].

Process-of-care variables that affect pharmacokinetics. Vancomycin pharmacokinetic indices were evaluated by Jeffres et al. [22] in 102 patients with health care–associated MRSA pneumonia enrolled in a study over a period of 6.5 years. In this retrospective analysis, vancomycin trough concentrations and the area under the concentration-time curve (AUC) values showed significant correlation. Hospital mortality rates were not different between the groups with low ($<15$ µg/mL; $n = 68$) and high ($\geq 15$ µg/mL; $n = 34$) trough concentrations. Stratification of AUC values also did not yield an association with hospital mortality rates. The authors speculated that, because optimization of vancomycin pharmacokinetic parameters did not improve hospital mortality rates, aggressive dosing strategies might not offer a therapeutic advantage [22]. However, process-of-care variables, including the need for mechanical ventilation or vasopressor therapy, were correlated with significantly higher mortality rates ($P < .001$) [22]. The relationship between vancomycin concentrations and clinical outcomes deserves more study.

VANCOMYCIN TOXICITY

Nephrotoxicity. The effect of vancomycin on kidney function is somewhat controversial; in the past, vancomycin toxicity was attributed to manufacturing impurities [18]. Then, a number of retrospective studies suggested that elevated serum concentrations of vancomycin were correlated with renal damage; however, the definitions of nephrotoxicity were variable, and serum vancomycin concentrations were often measured after the detection of increases in serum creatinine levels, making
the causal relationship unclear [18]. Hidayat et al. [13] plotted the incidence of nephrotoxicity due to vancomycin according to the concentration of vancomycin achieved (low, <15 μg/mL; high, ≥15 μg/mL). Nephrotoxicity occurred significantly more often in patients with high vancomycin trough concentrations than in those with low trough concentrations (12% vs. 0%; P = .01), and it was also associated with underlying renal disease. Concomitant therapy with nephrotoxic agents (P < .001), high trough concentrations of vancomycin (P = .03), and the duration of vancomycin therapy (P = .004) are significant predictors of nephrotoxicity [13]. It is thought that vancomycin can potentiate the nephrotoxic effect of other drugs, including aminoglycosides [18]. Recently, Micek et al. [23] also showed that nephrotoxicity was significantly associated with high trough concentrations of vancomycin (≥20 μg/mL; P = .002), although very few of these patients received concomitant treatment with other nephrotoxic agents.

“Red man syndrome.” Vancomycin is also known to produce hypersensitivity reactions, including anaphylaxis and “red man syndrome,” an infusion-related reaction characterized by pruritus and an erythematous rash [24]. The reported incidence of red man syndrome varies from 3.7% to 47%, and the most severe reactions occur in patients <40 years of age. Studies have also indicated that greater toxicity occurs when vancomycin is administered via rapid infusion (1 g in <1 h) [25]. In a randomized, double-blind, 2-way crossover study of 10 adults, infusion of 1 g of vancomycin for 1 h versus infusion for 2 h was associated with a significantly higher incidence and severity of red man syndrome (P < .05), greater peak concentrations of histamine release (P = .004), and greater total release of histamine (P = .017) [25].

**MONITORING SERUM LEVELS OF VANCOMYCIN**

Monitoring of serum levels of vancomycin may be quite useful in clinical practice to help ensure that adequate drug concentrations are reached. The standard vancomycin dosing regimens (500 mg every 6 h or 1 g every 12 h) were chosen somewhat arbitrarily for use in clinical trials, because there have been no formal studies to evaluate the relationship between serum concentrations and treatment outcome [1]. Many clinicians desire information about serum concentrations to adjust the dose of vancomycin, particularly in patients with renal impairment. Dosing nomograms may be helpful with dosing in patients with renal failure [26].

A recent retrospective pharmacokinetic analysis of serum levels of vancomycin determined during routine monitoring of 46 patients in a medical ICU concluded that standard dosages of vancomycin led to a 33% risk of not achieving the recommended area under the concentration-time curve over 24 h/MIC breakpoint for *S. aureus* [27]. Monitoring serum concentrations may be necessary to maximize efficacy, minimize toxicity, and reduce the emergence of resistance, because, in the past, underdosing may have contributed to the emergence of resistant strains over the years. The issue of monitoring serum levels remains controversial.

**CONCLUSIONS**

Recent years have seen the emergence of staphylococci that are resistant to vancomycin and the development of several newer antibiotics that are effective in the same arena as vancomycin. The changing susceptibility of staphylococci has led the Clinical and Laboratory Standards Institute to lower the breakpoint for vancomycin MICs from 4 μg/mL to 2 μg/mL, and some believe that the breakpoint should be even lower. In addition, information about the association of vancomycin with clinical outcome suggests that a change in dosing strategy may be needed. At the least, serum trough concentrations of vancomycin should be monitored. Older recommendations suggest that the trough levels should be no lower than 5–10 μg/mL [18], but newer information suggests that they should be >15 μg/mL [13]. Unfortunately, the data on MRSA infections remain limited for newer drugs as well as for vancomycin. Until more data become available to guide antibiotic selection, it is important for clinicians to be aware of the potential limitations of vancomycin as well as its strengths.

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