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AN COMPREHENSIVE REVIEW ON PHARMACOLOGICAL SIGNIFICANCE OF VANCOMYCIN ANTIBIOTIC

Prateek Porwal[1], Dr. Satish Kumar Sharma[2*]

[1]PhD Research Scholar, Glocal School of Pharmacy, The Glocal University, Mirzapur Pole, Saharanpur - 247001, Uttar Pradesh, India.
[2*]Professor & Dean, Glocal School of Pharmacy, The Glocal University, Mirzapur Pole, Saharanpur - 247001, Uttar Pradesh, India.

***Corresponding Author:** Satish Kumar Sharma
*Professor & Dean, Glocal School of Pharmacy, The Glocal University, Mirzapur Pole, Saharanpur - 247001, Uttar Pradesh, India, Email: satishdipsar55@gmail.com

Abstract
Since the late 1950s, vancomycin has been used extensively. Even if numerous helpful new anti-Gram-positive drugs have been developed recently and staphylococci are becoming less susceptible to methicillin, vancomycin is still the gold standard for treating bacteraemia caused by methicillin-resistant staphylococci. Vancomycin has clear dose-response and dose-toxicity connections. With a clinical cut-off of 400 for target values, the AUC/MIC model is widely accepted to be the most accurate predictor of these connections. In addition to ignoring other important vancomycin resistance-related problems, such as biofilm resistance and the inoculum effect, this model's experimental basis is weaker than is often believed. Vancomycin's current dose recommendations are for intermittent dosing with target attenuation values between 15 and 20 mg/L. Dosage modifications depending on renal function have been proposed but not yet confirmed. Clinical studies further support the use of continuous infusion at target plateau values of 20–25 mg/L, with reduced nephrotoxicity but equivalent effectiveness. The optimal dosage strategy for vancomycin that balances the high requirements for the dose-response link and the major drawbacks for the dose-toxicity relationship remains to be found, despite decades of rigorous clinical use and a wealth of research and papers. Streptococcus orientalis produces the tricyclic glycopeptide antibiotic known as vancomycin (VCM). It is commonly used in hospitals and is recommended to combat serious infections brought on by Gram-positive bacteria, particularly in light of the emergence of penicillin-resistant pneumococci and MRSA (methicillin-resistant Staphylococcus au reus). Additionally, it can be used to treat people who are allergic to cephalosporins and penicillins. In addition to being contentious, infusion kinds, dilution rates, and dosage recommendations might have harmful side effects. This paper's objective was to conduct a literature evaluation that demonstrated vancomycin's therapeutic and harmful effects.

Keywords: vancomycin, biofilm resistance, dosing, continuous infusion, staphylococci

Introduction

Originally introduced in 1956, vancomycin was intended to "vanquish" forms of Staphylococcus aureus that had become resistant to naturally occurring penicillins. When the antibiotic was initially created, there was an incredible amount of fervor and optimism for the future, which is nearly

unthinkable for current doctors. The list of regulatory criteria for the development of new antibiotics seemed to go on forever. and advertising were limited, and complex problems with pharmaceuticals and resistance had not yet surfaced.

Appropriate cures for all infectious diseases were near. Vancomycin but soon lost popularity, mostly due to frequent side effects associated with product impurities (the drug was commonly referred to as "Mississippi mud") and the development of cephalosporins and penicillins that were resistant to penicillinase. One Beginning in the early 1980s, methicillin-resistant S. aureus (MRSA) gradually expanded across hospitals, eventually reintroducing vancomycin into the general population. Image 2 Vancomycin's use as a first-line therapy for methicillin-non-susceptible staphylococci is now called into question due to the advent of vancomycin intermediate-susceptible S. aureus strains (VISA) and hetero-VISA (hVISA).3 and problems with toxicity.[4,5] The persistent rise in the vancomycin resistance index (MIC) among susceptible staphylococci is one significant problem. However, a recent study indicates that experimental variation between tests conducted at different times may make it difficult to spot patterns in MIC values when analyzing historical data. Six It has been discovered that the presence of severe underlying conditions and infections with a high concentration of bacteria, such as endocarditis, contaminated prosthetic devices, or deeply drained abscesses, as well as previous vancomycin treatment and MRSA infection, are risk factors that can result in VISA and hVISA infections.3. Vancomycin-resistant enterococci have also become more prevalent as a result of inappropriate usage of the antibiotic.[7]. Because of this, the CDC Hospital Infection Guidelines were created by the Control Practices Advisory Committee for its appropriate application.8 Vancomycin should only be used in the following circumstances, per these guidelines: MRSA and methicillin-resistant Staphylococcus epidermidis infections; methicillin-susceptible S. aureus (MSSA) infections in penicillin-allergic subjects; pseudomembranous colitis (in the event of a relapse or failure to respond to metronidazole treatment); endocarditis prophylaxis after high-risk procedures in penicillin-hypersensitive subjects; and surgical prophylaxis for major procedures involving the implantation of prosthetics in hospitals with a high prevalence of MRSA. As a result, the Control Practices Advisory Committee developed the CDC Hospital Infection Guidelines for its proper implementation [8]. Vancomycin should only be used in the following circumstances, per these guidelines: MRSA and methicillin-resistant Staphylococcus epidermidis infections; methicillin-susceptible S. aureus (MSSA) infections in penicillin-allergic subjects; pseudomembranous colitis (in the event of a relapse or failure to respond to metronidazole treatment); endocarditis prophylaxis after high-risk procedures in penicillin-hypersensitive subjects; and surgical prophylaxis for major procedures involving the implantation of prosthetics in hospitals with a high prevalence of MRSA. Recently, the situation has improved with the development of new agents (ceftobiprole, tigecycline, daptomycin, and linezolid); however, there is currently no evidence-based alternative reference standard agent for the treatment of serious infections with methicillin-resistant organisms.

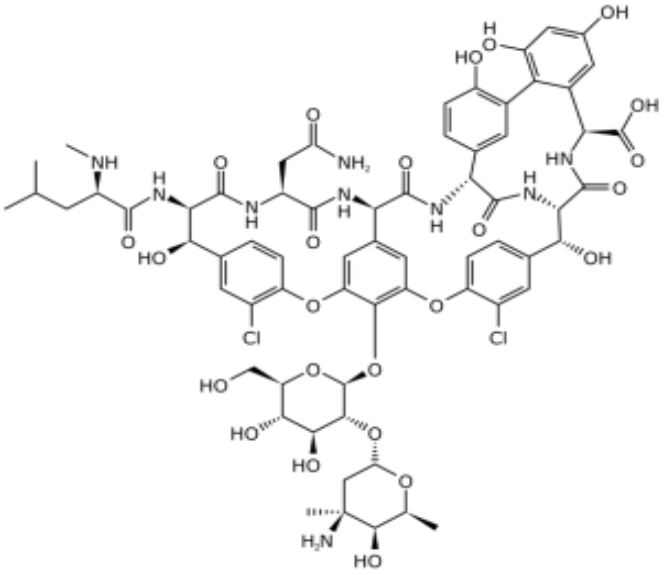
Summary of Vancomycin

Numerous original studies and reviews have contributed to a steady increase in our knowledge of the drug's toxicity and mechanism of action. Vancomycin unquestionably lacks the qualities of the ideal antibiotic. This large molecule should only be given intravenously [1]. When administered, vancomycin has a complex concentration-time curve. One Elimination, which approximately translates to creatinine clearance, is essentially the function of the kidneys. [5,10] Vancomycin is abundant in the body, but its penetration in many tissues is surprisingly low. In uninflamed meninges, its serum concentrations range from 0% to 18%, while in inflamed meninges, it ranges from 36% to 48%. In the lung, it can reach a maximum of 41% to 51%, and in diabetic patients, healthy soft tissues, and skin, it ranges from 10% to 30% [4].

Vancomycin works slowly by preventing the incorporation of murein monomers into the developing peptidoglycan, which ultimately results in osmotic cytolysis after a 24-hour delay [1.11]. Low-grade vancomycin resistance in VISA species is caused by the antibiotic gradually plugging into a thicker staphylococcal cell wall. Twelve Vancomycin's bactericidal efficacy is limited in cases of biofilm-

associated infections (known as biofilm resistance) and when the inoculum is large (known as the inoculum effect) [11].

Several lines of evidence suggest that β-lactam antibiotics are more effective than vancomycin in treating severe MSSA infections. [14,15] Vancomycin has a well-established dose-toxicity relationship, with the primary clinical concerns being nephrotoxicity and ototoxicity. It also has a unique dose-response relationship that is not reducible to a simple time above MIC (T.MIC). [4,16] Despite the abundance of pharmacodynamic/pharmacokinetic (PK/PD) modeling data, some important concerns remain regarding the relationships between dose, toxicity, and response. [4,10]



Mechanism of Action Vancomycin

The suppression of bacterial cell wall production, or more precisely, the inhibition of peptidoglycan formation, is how this antimicrobial drug works. For bacteria that reproduce, it is consequently bactericidal.

Peptidoglycan, which surrounds the whole bacterium, is found in the bacterial cell wall [4]. This material is more prevalent in Gram-positive bacteria, where it forms huge, insoluble layers on the outside portion of the cell membrane. These layers can reach 40 layers and are made up of many skeletons of amino sugars, including N-acetylglucosamine and N-acetyl muramic [4]. The latter forms a high-level resistant polymeric chain4 and is composed of cross-linked lateral short peptide residues. The medication blocks this polymerization or the transglycosylase process when it binds with high affinity to the C-terminal D-alanyl D-alanine residues of lipid-linked cell wall precursors and breaks the bond to the glycopeptide polymer [1].

Consequently, it stops peptide cross-links from attaching to tetrapeptide side chains, specifically, it stops it from attaching to the expanding tip of the peptidoglycan [4].

Antibacterial Activity

Gram-positive bacteria are specially treated with vancomycin; strains of these bacteria are considered sensitive if the minimum inhibitory concentration is less than 4 μg/ml [1]. Bacillus, Actinomyces, Clostridium, Corynebacterium [1], Staphylococcus aureus, S. epidermidis, S. pyogenes, S. pneumoniae, and Streptococcus viridans are among the species that it is typically successful against. Nonetheless, a sizable fraction of mycobacteria, fungi, and Gram-negative bacilli are vancomycin-resistant [1,3].

MRSA (methicillin-resistant Staphylococcus aureus) and penicillin-resistant pneumococcal infections1 have increased the importance of this antibiotic, in addition to other bacterial resistance mechanisms against β-lactam antibiotics. [24]

Therapeutic Use

Vancomycin hydrochloride is often given intravenously in hospitals and can be purchased commercially as sterile powder for dilution1,18. Guidelines suggest a 2.5–5.0 mg/mL dilution [3].
Hospitals often provide intravenous vancomycin hydrochloride, which is also available commercially as sterile powder for dilution1,18. A dilution of 2.5–5.0 mg/mL is recommended per guidelines.

- For newborns, start with 15 mg/kg and then 10 mg/kg every 12 hours throughout the first week of life.[1]
- 15 mg/kg, then 10 mg/kg every 8 hours for infants aged 8 to 30 days. [1]
- 10 mg/kg every 6 hours for older kids and babies [1]
- Children who have bacterial endocarditis should receive 20 mg/kg over a period of one to two hours. Thirty minutes before the procedure starts, the infusion must be stopped [3]

Little is known regarding the pharmacological effects or safety of this medication in pediatric patients, particularly in neonates, and standard dosages, infusion dilution, rate, and type (continuous or intermittent deliveries) are still debatable.[18-22].

Patients with reduced renal function should use this drug very carefully. The chances of nephrotoxicity and ototoxicity, among other side effects, should be reduced by modifying dosages and closely monitoring such individuals [3].

Posology, Efficacy and Toxicity

There are still unresolved issues with the 2009 publication of the International Consensus Guidelines, which sought to optimize vancomycin dosing and therapeutic monitoring. However, vancomycin has been utilized extensively in many health facilities despite the widespread worry and impression of elevated MICs, treatment failures, and its toxicity [20].
According to some research, the suggested dosages outlined in published guidelines are not always sufficient since they do not promptly raise therapeutic serum levels in people with normal renal function.9.25. There is no optimal standard dose of vancomycin, according to other recent studies, and the prescribed amounts should only be used to begin antimicrobial bial treatment. [7,26]. However, Giachetto et al. [27] point out that children in critical condition have different pharmacokinetic parameters.
Therefore, from the start of vancomycin treatment, important steps should be taken to ensure safe and effective drug administration, particularly in children and newborns: therapeutic monitoring, dosage individualization, establishing optimal doses, and renal function evaluation[1,3,9,10-14]. On the other hand, the use of insufficient dosages and extended therapy raise the possibility of toxic and sub therapeutic drug levels, which promote the growth of resistant microbes and the beginning of side effects. [1,3,7,9-14,26,27].

Vancomycin Adverse Effects

In addition to its side effects, which include tachycardia and hypotension, phlebitis, nephrotoxicity, ototoxicity5, chills, ex anthema, fever [1], and a significant risk of peripheral IV problems, vancomycin is not a first-choice medication. Furthermore, as previously stated, there is still debate on worldwide consensus guidelines for the prudent use of vancomycin, and little is known about the drug's safety [18–22]. The use of insufficient dosages and prolonged therapy is therefore documented in the literature, which raises the risk of toxic levels and the beginning and exacerbation of side effects [1,3,9-14].

Hypersensitivity Reaction

The medications that are most frequently linked to hypersensitivity responses include antimicrobials and anticonvulsants. All medications, though, have the potential to have these effects28. Both immunological and non-immune processes may cause these responses, and one of the main changes

is cutaneous manifestation. When cutaneous lesions are widespread or impact many organs, they are categorized as severe. Among the most serious causes are acute exanthematic pustulosis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug hypersensitivity syndrome.[28].

Ototoxicity

The use of vancomycin has been linked to several incidences of hearing loss, according to the literature. The drug's direct harm to the auditory branch of the eighth cranial nerve serves as the basis for the process. The high drug concentrations in the plasma (60 to 100 µ/ml) are directly linked to irreparable harm in certain circumstances. However, the majority of patients had pre-existing hearing loss or renal impairment, or they were even untreated with other ototoxic medications.[1,29,30]. Vancomycin should thus not be used in people who have already been diagnosed with hearing loss. Seldom reported adverse effects include vertigo, dizziness, and tinnitus; nonetheless, tinnitus may be a sign prior to hearing loss, necessitating a prompt interruption of medication administration.[1,29,30].

Nephrotoxicity

Between 20 and 25 percent of the cardiac output is sent to the kidneys. This translates to 1.100 ml/min, enabling a high rate of glomerular filtration that is essential for controlling solute concentrations and bodily fluid amounts [31].

In many nations, kidney diseases—whether severe or mild—are one of the leading causes of mortality and disability. Renal insufficiency, the term used to describe kidney abnormalities, may result from many of its severe forms, which can impact the renal interstitium, glomeruli, tubules, and blood vessels.[31].

Since glycopeptide antibiotics, such as vancomycin, are well recognized to be hazardous, their usage should be indicated with extreme precision. Patients who exhibit hypersensitivity reactions to beta-lac tam antibiotics or those with severe illnesses are typically appropriate for treatment with this family of medications40. In the past, the first documented cases of vancomycin nephrotoxicity were linked to contaminants discovered during the drug's manufacturing process. Renal lesions have been linked to alternative pathways as a result of improvements in the manufacturing process and the progressive elimination of contaminants from medications [41]. Although these mechanisms of action are unclear, research indicates that 7–17% of individuals receiving the medication intravenously for methicillin-resistant Staphylococcus aureus (MRSA) infections have nephrotoxicity [40].

Conclusions:

Vancomycin's story does not seem like that of a vanquisher, even after more than 55 years of widespread clinical usage. Although vancomycin is by no means the finest antibiotic available, it is still the best choice in many clinical scenarios.9. Hospitals continue to employ vancomycin, an antibiotic that has been effective for the past 55 years. However, there is still debate about dosage recommendations, dilutions, monitoring, infusion types, and rates regardless of how long this medication has been used therapeutically. Each of these elements has a part in the development of adverse effects associated with vancomycin usage.

As a result, much remains unknown regarding the pharmacology and, most importantly, the safety of this antibiotic. Therefore, in order to provide a safe and customized drug administration, it is crucial to define the optimal dosages, dilutions, infusion types and rates, therapeutic and clinical monitoring, and renal function evaluation from the start of the treatment. However, using insufficient dosages and extending treatments raises the possibility of toxicity and the beginning of negative side effects. Given this, further prospective double-blind randomized trials should be carried out to determine the true safety of vancomycin.

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