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A Review of Vancomycin for Treatment of Gram-Positive Bacterial Infections

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ABSTRACT:
Vancomycin is one of only a few antibiotics available to treat patients infected with methicillin-resistant Staphylococcus aureus and methicillin-resistant, coagulase-negative Staphylococcus species. Therefore, under standing the clinical implications of the pharmacokinetic and pharmacodynamic properties of vancomycin is a necessity for clinicians. Vancomycin is a concentration-independent antibiotic (also referred to as a "time dependent" antibiotic), and there are factors that affect its clinical activity, including variable tissue distribution, inoculum size, and emerging resistance. This article reviews the pharmacokinetic and pharmacodynamic data related to vancomycin and discuss such clinical issues as toxicities and serum concentration monitoring.

KEY WORDS: Vancomycin, Vancocin, Vancogen, Anti bacterial agent (Antibiotic)

I. INTRODUCTION:

Vancomycin is a large medication used in the treatment of serious Gram-positive bacterial infections. It is in the cell wall synthesis inhibitor class of antimicrobial medications. This activity reviews the indications, action, and contraindications for vancomycin as a valuable antimicrobial in treating Gram-positive bacterial infections. This activity will highlight the mechanism of action, adverse event profile, pharmacokinetics, and drug interactions pertinent for members of the interprofessional team in the treatment of patients with clinically significant Gram-positive bacterial infections.(1)

Structure of Vancomycin:

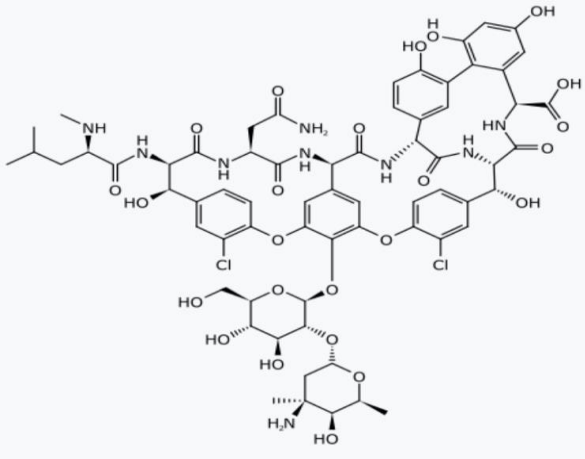

Fig 1: Vancomycin

Molecular formula: $C_{66}H_{75}Cl_2N_9O_{24}$
Molar mass: 1449.27 g·mol^{-1}

Indications:
Vancomycin is a tricyclic glycopeptide antibiotic originally derived from the organism *Streptococcus orientalis*. Vancomycin is used to treat and prevent various bacterial infections caused by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also effective for streptococci, enterococci, and methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. Vancomycin has numerous FDA-approved and off-label clinical uses.

Medical uses:
Vancomycin is indicated for the treatment of serious, life-threatening infections by Gram-positive (aerobic and/or anaerobic) bacteria unresponsive to other antibiotics.
The increasing emergence of vancomycin-resistant enterococci has resulted in the

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development of guidelines for use by the centres for disease control Hospital Infection Control Practices Advisory Committee. These guidelines restrict use of vancomycin to these indications:

- Treatment of serious infections caused by susceptible organisms resistant to penicillins (methicillin-resistant *S. aureus* (MRSA) and multidrug-resistant S.epidermidis (MRSE)) or in individuals with serious allergy to penicillins.
- Treatment of pseudomembrous colitis caused by *C. difficile*; in particular, in cases of relapse or where the infection is unresponsive to metronidazole treatment (for this indication, vancomycin is given orally, rather than by its typical intravenous route).
- For treatment of infections caused by Gram-positive microorganisms in patients with serious allergies to beta-lactam antimicrobials.
- Antibacterial prophylaxis for endocarditis following certain procedures in penicillin-hypersensitive individuals at high risk.
- Surgical prophylaxis for major procedures involving implantation of prostheses in institutions with a high rate of MRSA or MRSE.
- Early in treatment as an empiric antibiotic for possible MRSA infection while waiting for culture identification of the infecting organism.
- Halting the progression of primary sclerosing cholangitis and preventing symptoms; vancomycin does not cure the patient and success is limited.
- Treatment of endophthalmitis by intravitreal injection for gram-positive bacteria coverage. It has been used to prevent the condition, however, is not recommended due to the risk of side effects.[2]

Spectrum of susceptibility

Vancomycin is considered a last resort medication for the treatment of sepsis and lower respiratory tract, skin, and bone infections caused by Gram-positive bacteria. The minimum inhibitory concentration susceptibility data for a few medically significant bacteria are:

- *S. aureus*: 0.25 µg/mL to 4.0 µg/mL
- *S. aureus* (methicillin resistant or MRSA): 1 µg/mL to 138 µg/mL
- *S. epidermidis*: ≤0.12 µg/mL to 6.25 µg/mL

Side effects:

Oral administration

Common side effects associated with oral vancomycin administration (used to treat intestinal infections) include:

- gastrointestinal adverse effects (such as abdominal pain and nausea);
- dysgeusia (distorted sense of taste), in case of administration of vancomycin oral solution, but not in case of vancomycin capsules.

Intravenous administration

Serum vancomycin levels may be monitored in an effort to reduce side effects, although the value of such monitoring has been questioned. Peak and trough levels are usually monitored, and for research purposes, the area under the concentration curve is also sometimes used. Toxicity is best monitored by looking at trough values.

Common adverse drug reactions (≥1% of patients) associated with intravenous (IV) vancomycin include:

- Pain, redness, or swelling at the injection site;
- Vancomycin flushing syndrome (VFS), previously known as red man syndrome .
- Thrombophlebitis, which is common when administered through peripheral catheters but not when central venous catheters are used, although central venous catheters are a predisposing factor for upper-extremity deep-vein thrombosis..[3]

Mechanism of action:

Vancomycin is a glycopeptide antibiotic that exerts its bactericidal effect by inhibiting the polymerization of peptidoglycans in the bacterial cell wall. The bacterial cell wall contains a rigid peptidoglycan layer with a highly cross-linked structure composed of long polymers of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG). Vancomycin binds to D-alanyl D-alanine, which inhibits glucosyltransferase (peptidoglycan synthase) and the P-phospholipid carrier, thereby preventing the synthesis and polymerization of NAM and NAG within the peptidoglycan layer. This inhibition weakens bacterial cell walls and ultimately causes leakage of intracellular components, resulting in bacterial cell death. Vancomycin is only active against gram-positive bacteria.[4]

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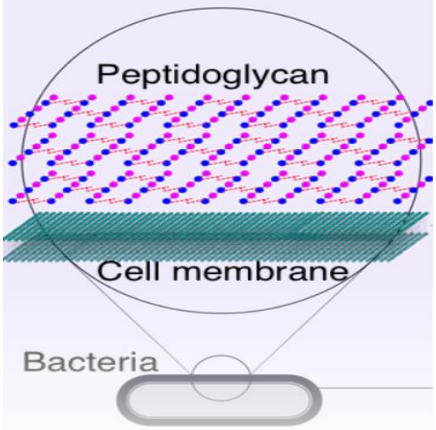

Fig 2 : Mechanism of action

Route of Administration:
Mostly by oral and IV administration

Intravenous
Vancomycin must be given intravenously (IV) for systemic therapy, since it is poorly absorbed from the intestine. It is a large hydrophilic molecule that partitions poorly across the gastrointestinal mucosa.Due to short half-life, it is often injected twice daily.

Oral
The only approved indication for oral vancomycin therapy is in the treatment of pseudomembranous colitis, where it must be given orally to reach the site of infection in the colon. Following oral administration, the faecal concentration of vancomycin is around 500 µg/mL (sensitive strains of clostridium difficile have a mean inhibitory concentration of ≤2 µg/mL).

Inhaled
Inhaled vancomycin can also be used off-label, via nebuliser, for the treatment of various infections of the upper and lower respiratory tract.

Rectal
Rectal administration is an off-label, use of vancomycin for the treatment of clostridium difficile infection.[5]

Tissue distribution:
Vancomycin penetrates into most body spaces, al though the concentrations obtained are variable and somewhat dependent on the degree of inflammation present. In studies examining the penetration of vancomycin into the CSF of patients with uninflamed meninges, fairly low concentrations have been demonstrated (range, 0–3.45 mg/L), with corresponding CSF-to-serum ratios of 0–0.18. As expected, inflamed meninges improve penetration of vancomycin into the CNS, with reported concentrations of 6.4–11.1 mg/L and CSF-to-serum ratios of 0.36–0.48. The penetration of vancomycin into the lung is highly variable.
Investigated the penetration of vancomycin into the lung tissue of 36 patients undergoing a partial lobectomy. After intra venous administration of 1 g of vancomycin, concentrations ranged from 0 to 12.2 mg/L, with a mean con centration of 2.8 mg/L and a penetration of 41%. In a recent study investigating the penetration of vancomycin into the epithelial lining fluid of healthy volunteers given 1 g of vancomycin every 12 h, the mean concentration at 12 h was 2.4 mg/L, which represented a 52% overall penetration rate.
However, in critically injured patients, penetration of vancomycin into epithelial lining fluid was more variable, ranging from 0 to 8.1 mg/L after several hours, with an overall blood to–epithelial lining fluid penetration ratio of 6:1.
Although the activity of oritavancin was comparable in both lung and thigh infection models, vancomycin activity was found to be 2–3-fold less potent in the lung infection model, compared with the thigh infection model.[6]

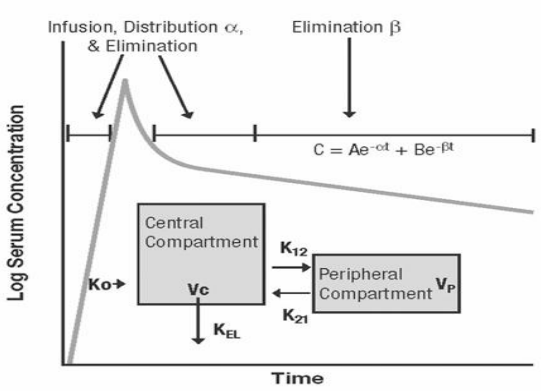

Fig 3 : Schematic representation of a 2-compartment pharmacokinetic model

Where,
C is the concentration
a and b are the respective elimination constants
e is the base of the natural logarithm, t is time
A and B are the respective zero time intercepts for a and b
Ko is the infusion rate constant
Vc is the volume of the central compartment
Vp is the volume of the peripheral compartment
K_{12} and K_{21} are intra compartmental rate constants
K_{EL} is the elimination rate constant from the central compartment.

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Pharmacokinetics:
Inhibition of bacterial growth: Slowly bactericidal
PK/PD parameter: AUC: MIC
Absorption: Oral vancomycin has a bioavailability of less than 10%.
Onset of action:
Vancomycin has a rapid onset of action with a serum peak concentration immediately following the completion of the intravenous infusion. The onset of action of oral vancomycin is currently unknown.

Distribution:
Large volume of distribution (0.4 L/kg to 1.0 L/kg) in body tissues and fluids, excluding cerebrospinal fluid (CSF) with non-inflamed meninges.
Protein Binding: Approximately 55%
Metabolism: No evident metabolism (excreted unchanged)
Clearance: 0.71 mL/minute/kg to 1.31 mL/minute/kg in adults with normal renal function.
Half-life:
Vancomycin has a bi-phasic elimination half-life, with its initial half-life being relatively quick and a terminal half-life of 4 to 6 hours in healthy adults with normal renal function. The elimination half-life is significantly prolonged in patients with renal dysfunction. Close monitoring is necessary for these patients.
Excretion:
Intravenous vancomycin injection is primarily eliminated by glomerular filtration in the kidney (75% via urine). Oral vancomycin predominantly gets excreted in faeces.[7]

Human Pharmacodynamic Studies

There are very few human studies evaluating the pharmacodynamics of vancomycin, and the findings of most of those studies have not been conclusive in determining which parameter has the most value in predicting patient outcome. The majority of studies have involved relatively small patient populations and patients with a variety of infection types. One prospective evaluation randomized 106 patients with S. aureus infections, including bacteremia and endocarditis, to achieve 3 different trough concentration targets of 5–10 mg/L, 10–15 mg/ L, and 15–25 mg/L. No relationships were found between peak concentrations, trough concentrations, or pharmacodynamic parameters (e.g., peak/MIC, time above the MIC,orAUC/MIC) and organism eradication or overall patient outcome.[8]

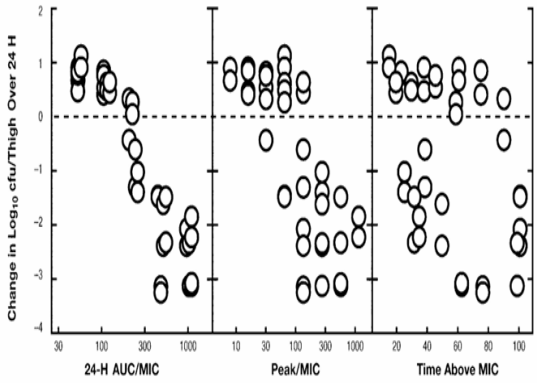

Fig 4 : Relationship between pharmacokinetic/pharmacodynamic indices for vancomycin and bacteriologic efficacy against methicillin-susceptible Staphylococcus aureus.

Contraindications:
Vancomycin is contraindicated in patients with a known hypersensitivity reaction to the drug or any component within the formulation.
Clinical Considerations
Although vancomycin does not have many contraindications, there are some important clinical considerations to keep in mind during patient care.

Geriatric Considerations

Elderly patients are more prone to vancomycin toxicity with IV administration due to age-related changes in renal function, volume of distribution, and accumulation. These patients need to be carefully monitored and require a more conservative dosage regimen.

Pregnancy Considerations

Oral vancomycin capsules are categorized as a category B drug for use in pregnancy. In contrast, intravenous vancomycin injection is category C. Vancomycin should not be used during pregnancy unless the benefits outweigh the risks of the medication. If treatment with vancomycin is necessary, close monitoring of maternal blood is recommended to reduce the risk of ototoxicity and nephrotoxicity in the foetus. Animal studies have not yet determined any evidence of fetal harm from maternal vancomycin use. However, vancomycin crosses the placenta, and researchers have detected it in fetal serum, amniotic fluid, and cord blood. Patients who become pregnant while taking vancomycin should contact their healthcare provider immediately. Moreover, it is essential to note that pregnant patients may require higher doses of vancomycin to achieve therapeutic

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concentrations due to alterations in pharmacokinetics, such as an increased volume of distribution and total plasma clearance.[9]

Breastfeeding Considerations

Vancomycin is excreted in breast milk following intravenous administration. In comparison, oral vancomycin has minimal systemic absorption and, therefore, limited excretion through breast milk. Breastfeeding mothers who receive intravenous vancomycin should consult with their provider before continuing, as it may affect their baby's health. Nevertheless, vancomycin is recommended to treat *Clostridioides difficile* infections in breastfeeding women. Careful assessment regarding the discontinuation of breastfeeding is recommended before initiating vancomycin therapy in nursing mothers.

Renal Impairment

The reduced renal function can cause vancomycin to accumulate in the body, thereby increasing the risk of adverse effects. Dosing adjustments are necessary for renal impairment. Close monitoring of vancomycin trough concentrations is necessary for all patients with renal impairment. Patients should receive counsel to contact their provider if they experience symptoms of reduced kidney function, such as decreased urine output, swelling, and abdominal pain, as vancomycin may exacerbate renal impairment.

Bacterial Resistance

As with other antimicrobials, prolonged or inappropriate treatment with vancomycin can lead to bacterial resistance, such as vancomycin-resistant enterococci (VRE). Providers need to be aware of increased antimicrobial resistance patterns and practice appropriate antimicrobial stewardship. Moreover, patients should receive counselling on the importance of medication adherence to prevent the development of multidrug-resistant infections.

Drug Interactions

Co-administration of other medications, along with vancomycin, may increase the risk of adverse effects and toxicity. Therefore dosing adjustments, additional monitoring, and consideration of alternative treatment should merit attention when combining vancomycin with certain medications. Caution is necessary when administering vancomycin with other nephrotoxic agents such as aminoglycosides, amphotericin products, and IV contrast.[10]

Therapeutic drug Monitoring:

Plasma level monitoring of vancomycin is necessary due to the drug's biexponential distribution, intermediate hydrophilicity, and potential for ototoxicity and nephrotoxicity, especially in populations with poor renal function and/or increased propensity to bacterial infection. Vancomycin activity is considered to be time-dependent; that is, antimicrobial activity depends on the duration that the serum drug concentration exceeds the minimum inhibitory concentration of the target organism. Thus, peak serum levels have not been shown to correlate with efficacy or toxicity; indeed, concentration monitoring is unnecessary in most cases. Circumstances in which therapeutic drug monitoring is warranted include: patients receiving concomitant aminoglycoside therapy, patients with (potentially) altered pharmacokinetic parameters, patients on heamodialysis,patients administered high-dose or prolonged treatment, and patients with impaired renal function. In such cases, trough concentrations are measured.

Target ranges for serum vancomycin concentrations have changed over the years. Early authors suggested peak levels of 30 to 40 mg/L and trough levels of 5 to 10 mg/L, but current recommendations are that peak levels need not be measured and that trough levels of 10 to 15 mg/L or 15 to 20 mg/L, depending on the nature of the infection and the specific needs of the patient, may be appropriate. Using measured vancomycin concentrations to calculate doses optimizes therapy in patients with augmented renal clearance.[11]

Toxicity

Nephrotoxicity and ototoxicity have correlations with the use of vancomycin.

Nephrotoxicity:

The proposed mechanism of nephrotoxicity is renal tubular ischemia due to the oxidative effect of vancomycin on cells of the proximal renal tubule. Common risk factors for nephrotoxicity include pre-existing renal impairment, concurrent use of nephrotoxic medications, advanced age, and dehydration. Although vancomycin-induced nephrotoxicity is commonly reversible, it can be challenging to differentiate it from acute interstitial nephritis and

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worsening renal function due to uncontrolled infection.

Ototoxicity:

Ototoxicity is a rare complication associated with vancomycin monotherapy. It is common in patients receiving excessive vancomycin doses, concurrent ototoxic medications (e.g., aminoglycosides, loop diuretics, antineoplastic agents), and those with underlying hearing loss conditions. Treatment should stop if patients experience signs of cytotoxicity, such as tinnitus, loss of hearing, and unbalanced movements.[12]

II. CONCLUSION:

In this review,vancomycin is an antibiotic used in the treatment of infections caused by multidrug-resistant Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus*. In the last decades, vancomycin has been widely used in hospital environments due to the increasing incidence of sepsis and septic shock. The results showed that vancomycin achieved pharmacodynamic coverage for MIC = 1 g/mL in high daily doses (≥3 g); for MIC = 2 g/mL to achieve the same therapeutic target, 6 g/day was required. Considering that high daily doses of vancomycin increase the risk of toxicity, we suggest the individual and monitored use of this antimicrobial to optimize PK/PD parameters, or when possible, the use of other antimicrobial agent with activity against these microorganisms.

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