SAFETY AND EFFICACY OF VANCOMYCIN THERAPY IN A TERTIARY CARE HOSPITAL - A PROSPECTIVE OBSERVATIONAL STUDY

Dissertation submitted to Kerala University of Health Sciences

In partial fulfilment of the requirements
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DOCTOR OF PHARMACY

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ABSTRACT

Vancomycin is widely used to treat infections caused by Gram-positive organisms. Its use is, however, associated with a number of clinically significant side effects. Careful supervision of drug administration and monitoring of serum concentrations are therefore required. Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicities, nephrotoxicity, and possible ototoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events. Its overall use was curtailed significantly with the development of semisynthetic penicillins (e.g., methicillin, oxacillin, nafcillin) that were considered less toxic. However, the steady rise in the number of MRSA infections since the early 1980s has once again brought vancomycin into the forefront as the primary treatment for infections caused by this organism.

This study focuses on the safety and clinical outcomes of vancomycin therapy in such cases in south Indian population. This prospective study conducted for 6 months may help the healthcare providers to ensure the judicious use of vancomycin in hospitalized patients.

AIM

To evaluate the safety and efficacy of vancomycin in hospitalized patients

OBJECTIVES

1. To analyze the safety of vancomycin in hospitalized patients
2. To analyze the clinical outcomes of vancomycin.
3. To document the duration, dose of vancomycin therapy and adverse effects if any.
4. To propose standard treatment guidelines of vancomycin therapy in hospital under the consultation with nephrology department.

METHODOLOGY

Study Design:

A prospective observational study is proposed to be conducted in the Lourdes hospital. Study population consists of patients who have given their consent to be a part of the study and meet the inclusion as well as exclusion criterias. will be based on the in-patients records from various departments for 6 months. Creatinine Clearance and other lab parameters, vancomycin therapy given to the patients (dose and duration), adverse effects if any and prescription guidelines are observed. Data collection will be done using a pre-designed data collection form. The data will then be assessed and categorized. Demographics, past medical history, past medication history, prescribed medications their dose, frequency and duration and lab parameters will be recorded.

Study Period

A six months study, the data collection was carried out from October 2022- April 2023.

STUDY SITE:

The study was conducted in the medical departments of Lourdes Hospital, Kochi – a tertiary care teaching hospital

METHOD OF SLECTION

Patients were selected based on inclusion and exclusion criteria.

Inclusion criteria:

1. Patients with age ≥18 years
2. Hospitalized patients who are on vancomycin therapy.

Exclusion criteria:

1. Patients with incomplete data
2. Patients who are discharged against medical advice
3. Patients with Creatinine Clearance ≤ 20 ml/min.

SAMPLE SIZE

A total of 60 patients who met the inclusion and exclusion criteria were selected in the study. (Minimum sample size required was found to be 60)

DATA COLLECTION METHOD

- Lourdes Mediware System
- Specially designed patient data collection form.
- Patient's medical record

STUDY METHOD

The prospective study was conducted in Cardiology department of Lourdes Hospital, Ernakulam.

RESULT AND DISCUSSION

We enrolled 60 patients. There was a male preponderance with in the study sample with 36 patients. There was not much difference in the age group with 47 adult patients and the remaining elderly patients. A significant number of meningitis were present in the study sample with 26 patients which remained the major indication of vancomycin therapy followed by 7 patients with bone infections. In order to evaluate the severity of nephrotoxicity AKIN criteria was used. It was found that 11.6% were under Stage 1 category and 5% were under stage 2 category. On analyzing the clinical outcome of treatment, we found that 100% cases there were favorable response, defined as complete or partial resolution of presenting signs and symptoms. All-cause mortality within 30 days of vancomycin therapy analysis revealed that 2 patients died. Among the study population 5% patient shows nephrotoxicity. There were mean value changes in pertinent laboratory values like total count, neutrophil, ESR, S.creatinine and urea. the mean days of therapy and length of stay of patients who were on vancomycin therapy was found to be 6.86 days and 12.23 days respectively. There was a statistically significant reduction in the neutrophil values before vancomycin therapy compared to the neutrophil values after vancomycin therapy and it also shows that there was a reduction in ESR value after vancomycin therapy compared to the baseline and it is significant statistically. This shows that the patient has recovered from the infection. There was slight elevation in creatinine and reduction in urea after vancomycin therapy it was statistically significant (p value =<0.001,p value= <0.045).

We also evaluated the distribution of doses and frequency for various diseases treated with vancomycin and dosing were in accordance with the standard guidelines.

We also categorized the disease conditions treated with vancomycin using AKIN criteria. 7 patients (11.6%)who were treated with vancomycin for Meningitis, Encephalitis UTI,Sepsis ,Bone infections under Stage 1 with creatinine level in the range of (1.5-2.3 mg/dl) and DM,HTN,CAD,melanoma were the risk factors About 3 patients (5%) treated with vancomycin for CRBI and sepsis fall under stage 2 (2.4-4 mg/dl) and Diabetes mellitus and hypertension were the risk factors identified for these patients The prevalence of adverse reactions to vancomycin observed in the study population were evaluated and out of 60, 19 patients encountered with ADR

CONCLUSION

Our study analyzed the safety and efficacy of vancomycin in hospitalized patients. Vancomycin associated nephrotoxicity were observed in 15.6% of study populations. Vancomycin administration resulted in favorable response of either partial or complete resolution of presenting signs and symptoms of infection were found in 90%. The doses prescribed for the study population were in accordance with standard guidelines. The adverse reactions due to vancomycin were observed in study population. Despite the occurrence of ADRs due to vancomycin use, it is an indispensable antibiotic to treat broad type of severe Infections. Guidelines for the judicious use of vancomycin was proposed on consultation with The Nephrology department.

INTRODUCTION

Methicillin-resistant Staphylococcus aureus (commonly known as MRSA) is a subset of bacterial (staph) infection of the skin The term "Staph" refers to the Staphylococcus aureus bacteria. Methicillin resistance, as well as resistance to other widely used antibiotics like amoxicillin, oxacillin, and penicillin, distinguishes MRSA from a regular staph infection. (1) This indicates that the infection is not treated by these drugs.

That is why treating an MRSA infection is so challenging. Community-associated MRSA (CA-MRSA) and health care-associated MRSA are the two main forms of MRSA (HA-MRSA). (2)

For serious infections caused by Staphylococcus aureus (MRSA), vancomycin trough concentrations of 15-20 mg/L are advised. Methicillin-resistant MRSA infections from Staphylococcus aureus are linked to high rates of death, morbidity, and medical expenses(3). An essential antibiotic for the management of invasive MRSA infections is vancomycin.

This anti-MRSA medication has the most clinical experience of any anti-MRSA medication when it comes to treating a range of invasive clinical syndromes, such as bacteremia, endocarditis, pneumonia, and osteomyelitis(4). However, because to sluggish bactericidal activity, the formation of resistance germs, and potential "MIC creep" among susceptible strains, its usefulness has been questioned. For treating methicillin-susceptible S. aureus bacteremia and infective endocarditis, vancomycin is less effective than -beta lactams. The degree of inflammation affects tissue penetration, which is highly varied. In particular, penetration is restricted for bone, cerebrospinal fluid, and lung epithelial lining fluid (5).

Vancomycin has traditionally been used as a first-line agent for treating methicillin-resistant Staphylococcus aureus (MRSA) as well as other Gram-positive beta-lactam–resistant bacteria which are common causes of serious health-related infections. Although the effectiveness of vancomycin is supported by more than 5 decades of use and numerous research, the clinical and microbiological context in which it is administered is always changing (6). Achieving an appropriate dosage of vancomycin for S.aureus infections might be challenging due to the clinical impact of the creep in the MIC of vancomycin and heteroresistance among MRSA strains, or due to complex pharmacokinetic and pharmacodynamic (PK/PD) circumstances. In this context, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases .Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) introduced a practice guideline in 2009 (7), marking a milestone in vancomycin therapy. However, a number of issues, such as the optimal dosing in some special clinical scenarios (e.g., with renal replacement therapies or in burn patients or who are obese), the role of continuous infusion, or the renal toxicity when the suggested vancomycin serum levels are reached, remain unanswered.

Dosing and monitoring strategies for intravenous vancomycin have been the subject of numerous worldwide guidelines and literature studies. Recent contributions to the literature have highlighted the necessity for a re-evaluation of guideline recommendations, in response to evolving understanding of goals for efficacy and toxicity in increasingly complicated patients. Based on in vitro animal and human studies, the pharmacokinetic or pharmacodynamic target for the treatment of S. aureus infections with intravenous vancomycin is the area under the total concentration-time curve (0-24 h) divided by the minimum inhibitory concentration (AUC24/MIC. The first human study to propose an AUC24/MIC target of 400 h derived this value from observational data from patients with S. aureus lower respiratory tract infections where the vancomycin MIC by broth microdilution (BMD) was 1 mg/L(9) . The expression AUC24/MIC should be changed to AUC24/MICBMD to represent the MIC determination method, because multiple validated techniques of MIC determination are not interchangeable. Guidelines and observational studies are in general agreement that this target has some validity and thus is a useful starting point for discussion about various approaches to dosing and monitoring, More recent observational studies have recognised that risk of toxicity also needs to be considered and have attempted to identify AUC24 thresholds associated with nephrotoxicity, leading to a proposed AUC24 upper limit of 700 (mg/L).h . Other factors include characteristics of the infection in each patients (e.g., site, severity, bacterial subtype, MIC), physiological status (such as renal function), and clinical progress.(10)

Vancomycin is a glycopeptide antibiotic with a history that can be traced back to the 1950s when it was discovered generated by Streptomyces orientalis in soil. It is one of the most frequently prescribed drugs, and for decades has been the primary treatment for patients with suspected or known antibiotic-resistant Gram-positive infections. The recommended pharmacokinetic-pharmacodynamic target AUC/MIC ratio for vancomycin is >400 (ie, the ratio of the area under the serum concentration time curve [AUC] to the minimum inhibitory concentration [MIC]). This is especially true for treating methicillin-resistant Staphylococcus aureus (MRSA) infections(11). To facilitate management and simplify vancomycin dose adjustments and monitoring, numerous organizations in 2009 suggested trough monitoring and maintaining trough concentrations between 15 and 20 µg/mL. Since these guidelines were

published, several studies have tested the efficacy and safety of suggested vancomycin trough concentration (VTC), with conflicting results. More recent research revealed that high VTC did not correlate with any notable improvement in treatment outcomes, for either adults nor children. Nephrotoxicity remains the most serious vancomycin-associated adverse effect, as reported by numerous studies, and is linked with high mortality, longer hospital stay, and higher medical expense(12). Although vancomycin is frequently associated with nephrotoxicity, the direct mechanisms are controversial. Multiple studies have focused on oxidative stress as a potential mechanism of nephrotoxicity, particularly when it affects the proximal tubule. Other research studies showed that vancomycin can change the energy-dependent renal reabsorption function of the proximal tubule cells and alter mitochondrial function, which is also linked with vancomycin-induced kidney damage(13).

Because of the potent bactericidal effect, Vancomycin is often used as a final resort in the case of ineffective use of other antigens. While due to the occurrence of adverse reactions, the use of vancomycin is strictly constrained. The primary adverse reactions of vancomycin include hypersensitivity reactions, nephrotoxicity, ototoxicity, and so on. The most typical manifestations of hypersensitivity reaction are hypersensitivity macular cutaneous rashes and anaphylaxis. Vasodilatation, bronchoconstriction, increased capillary permeability ,stimulation of autonomic nervous system , and mucosal hypersecretion are the major effects of vancomycin induced hypersensitivity reactions(14). One study showed that after vancomycin intravenously, 7%–17% of MRSA infected patients presented nephrotoxicity. The dose, duration, and plasma concentration of vancomycin are all closely correlated to the incidence of nephrotoxicity. Cases of hearing loss may be linked to vancomycin use because the drug directly damages auditory branch of the eighth cranial nerve. Additionally, some minor adverse reactions such as reversible neutropenia, reversible agranulocytosis, gastrointestinal symptoms, and pseudomembranous colitis should not be ignored. Vancomycin can produce two types of hypersensitivity reactions, the red man syndrome and anaphylaxis . Red man syndrome is an infusion-related reaction specific to vancomycin . It typically consists of pruritus, an erythematous rash that involves the face, neck, and upper torso. Hypotension and angioedema can occur less frequently. Patients commonly complain of generalized discomfort as well as diffuse burning and itching(15). They can rapidly become dizzy and agitated, and can develop headache, chills, fever, and paresthesia around the mouth. In severe

cases, patients complain of chest discomfort and dyspnea. In many patients, the syndrome is a mild, evanescent pruritus at the end of the infusion that goes unreported. Signs of red man syndrome would emerge 4–10 min after an nfusion started or may begin soon after its completion. It is often associated with rapid (<1 hour) infusion of the first ose of vancomycin(16). The reaction may not be of the same severity with subsequent exposures, but it can occur for ıe first time after multiple doses or during a slow infusion . Delayed reactions at or near the end of a 90 or 120 min ıfusion have been seen in patients who had been on vancomycin therapy for more than 7 days without prior incident. 'ancomycin must be given for at least 60 minutes according to the majority of hospital standards . Sporadic reports ›f red man syndrome after the administration of vancomycin via routes other than intravenously are also on the ncrease. Red man syndrome has been linked to intraperitoneal and oral administration of vancomycin .

.ed man syndrome was in the past attributed to impurities found in vancomycin preparations, earning the drug the ickname 'Mississippi mud'. However reports of the syndrome persisted even after improvements in the compound's ırity . Studies have shown that an unknown proportion of the population may be predisposed to releasing a large nount of histamine in response to vancomycin . (17). The hypersensitivity reactions that can arise due to vancomycin 'e due to its effect on the mast cells. In tissue culture, vancomycin induces degranulation of peritoneal mast cells in ats. The anaphylactic reaction is mediated by IgE. Red man syndrome, an anaphylactoid reaction, is brought on by ıe degranulation of mast cells and basophils, which results in the release of histamine without the aid of preformed ;E or complement. The extent of histamine release is partly correlated to the amount and rate of the vancomycin fusion. Clinical studies have demonstrated that the plasma tryptase levels were not significantly increased in ›nfirmed anaphylactoid reactions, so they can be used to distinguish chemical reactions from immunologic reactions 18).

VANCOMYCIN:

ORIGIN:

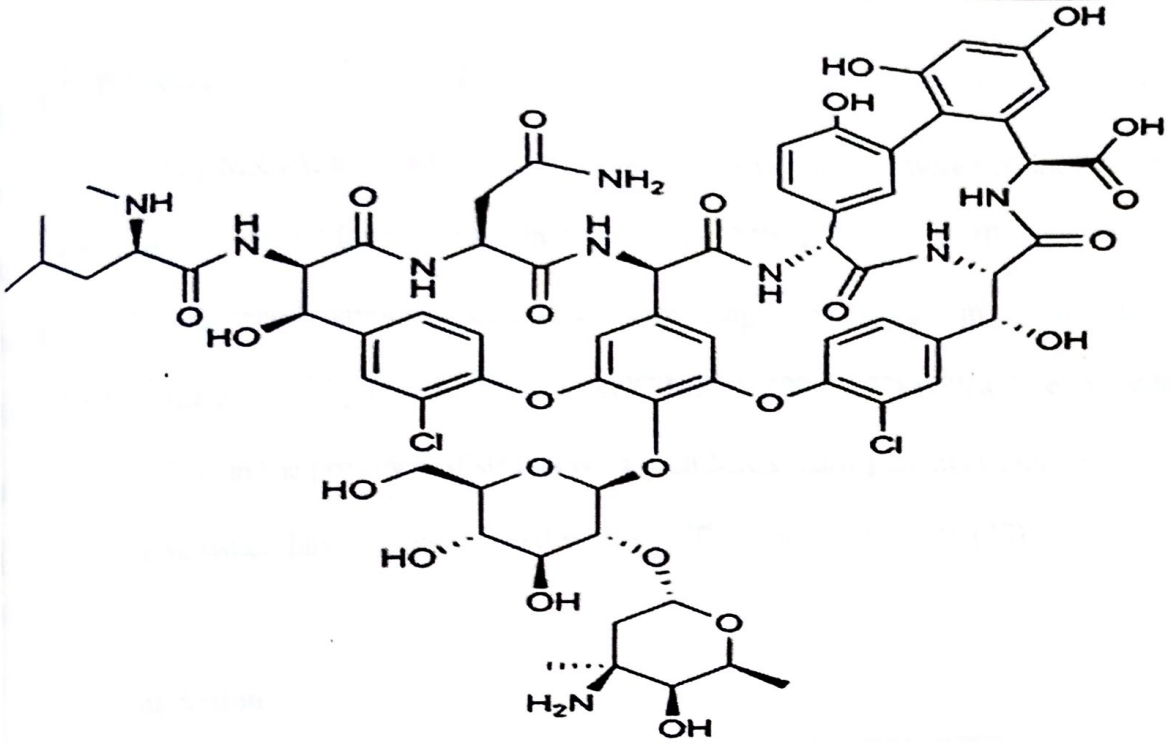
Vancomycin is a glycopeptide antibiotic discovered in 1956 as a penicillin substitute which assumed special ignificance due to efficacy against MRSA, Strep. viridans, Enterococcus and Cl. difficile.It is an antibiotic produced by treptococcus orientalis and Amycolatopsis orientalis. With the exception of Flavobacterium , it is active only against ram-positive bacteria. Vancomycin is a glycopeptide of molecular weight 1500. It is water soluble and quite stable(19).

listory and discovery

'ancomycin was isolated in 1957 by Dr. E.C Kornfield, an organic chemist with Eli Lilly in the deep jungles in Borneo 'om a fungus named Streptomyces orientalis.

'hemistry

'ancomycin structure consists of a seven-membered peptide chain forming a tricyclic ring system that has a isaccharide composed of vancosamine and glucose attached to it. The N-terminal amino acid leucine is critical for ntibacterial activity.



3.1 CHEMICAL STRUCTURE

Pharmacologic Properties

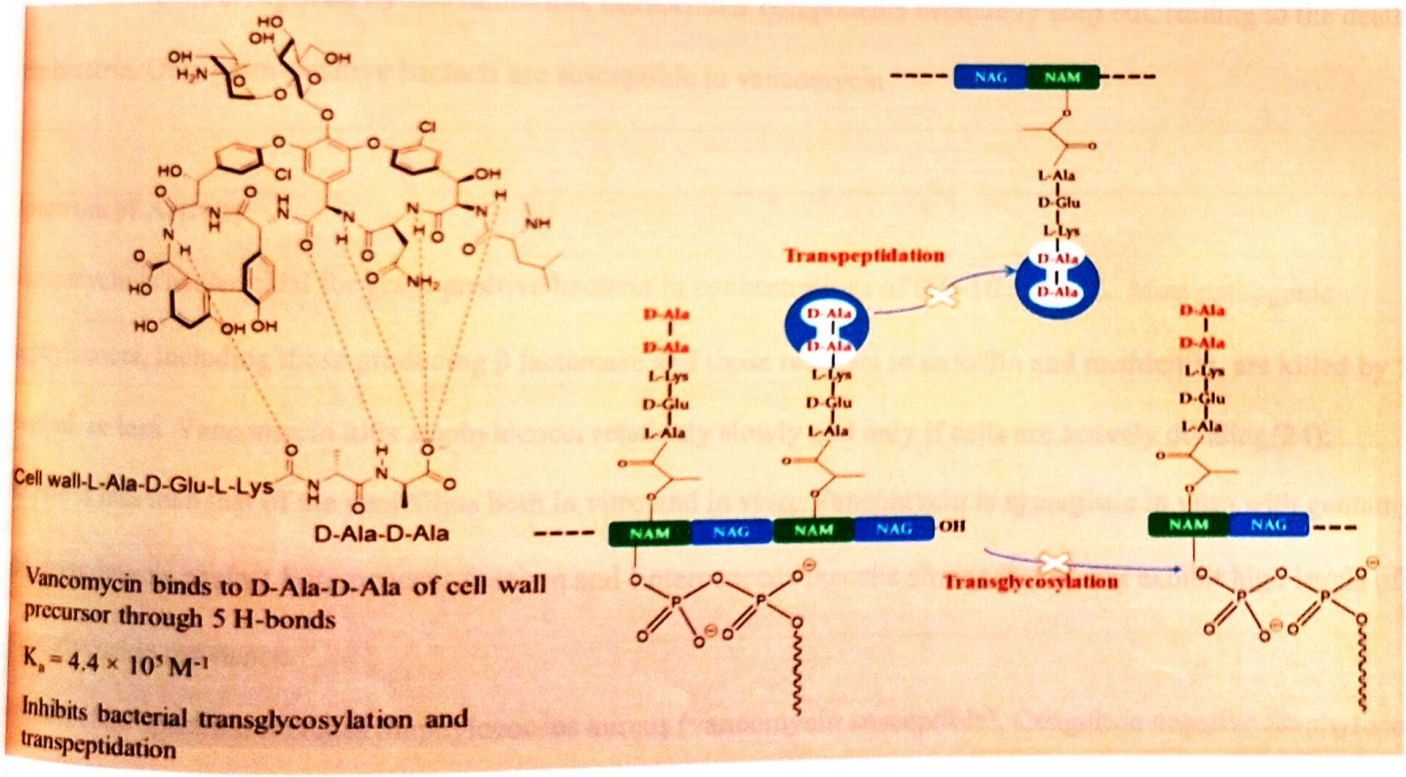
ts characteristic antibacterial spectrum against Gram-positive bacteria such as multidrug-resistant *E. faecalis*, *E.*
ecium, *Clostridium difficile*, and MRSA, with negligible anti-Gram-negative activity, complements the antibacterial
ectrum of the more popular third-generation cephalosporins and carbapenems. As empiric use of combination
herapy with vancomycin increased(20) , it was feared that the incidence of glycopeptide-intermediate-sensitive *S.*
ureus (GISA) (also called vancomycin-intermediate VISA strains) would arise. Thus, research into glycopeptides has
ocused on: enhancing activity against the GISA and VISA strains, including vancomycin-resistant enteroccocci
/RE); and improving pharmacological properties.

/ancomycin has a strong tendency to form multiple hydrogen bonds with itself in aqueous solution, making it an
eal drug in which to introduce a promoiety to generate a prodrug capable of efficient self-assembly to form

ydrogels. The best pharmacodynamic predictor of efficacy is the 24 h AUC/MIC ratio for example, in patients with neumonia caused by MRSA, a higher success rate and faster eradication were obtained when AUC/MIC ≥ 400(21). o correlation has been found for vancomycin between T > MIC and clinical efficacy.

harmacokinetic/pharmacodynamics (PK/PD) modeling using Monte Carlo simulations suggests that, for strains with a IC of 2 μg/mL, the probability of achieving an AUC/MIC > 400 is 57% with a dose of 2 g bid, and 15% with a dose f 1 g bid. Therefore, in the presence of strains with such MICs many patients should receive more than 4 g/day of ncomycin, a dose which has been associated with significant nephrotoxicity (22)

Mechanism of Action



.2 MECHANISM OF ACTION OF VANCOMYCIN

ancomycin is a glycopeptide antibiotic that exerts its bactericidal effect by inhibiting the polymerization of

peptidoglycans in the bacterial cell wall. This effect, which occurs at a site different from that affected by the penicillins, produces immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.

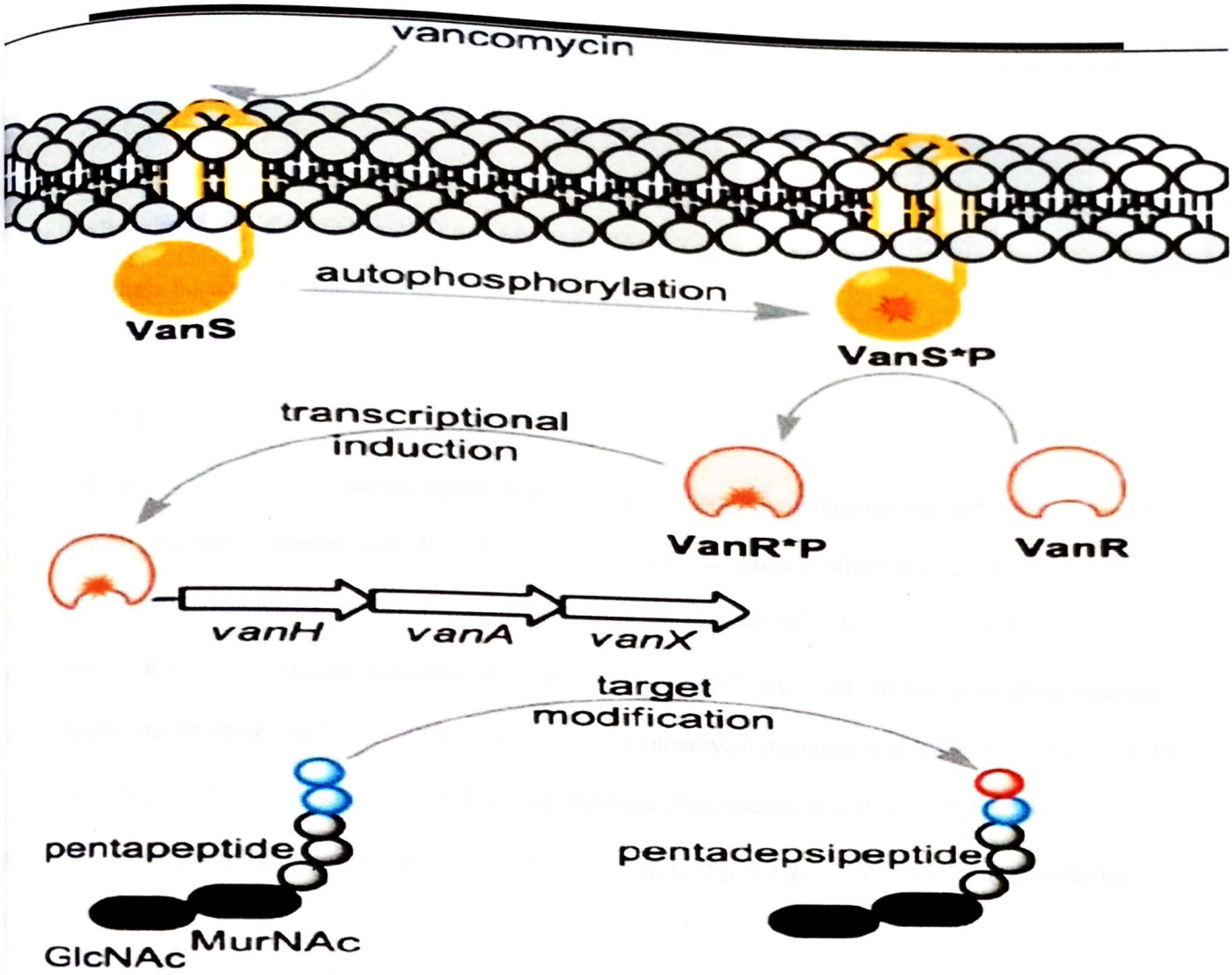
Magnesium, manganese, calcium, and ferrous ions reduce the degree of adsorption of vancomycin to the cell wall, but the in vivo importance of this interaction is unknown.

The peptidoglycan layer of the bacterial cell wall is stiff and has a strongly cross-linked structure made of long polymers of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) (NAG)(23). Vancomycin inhibits glucosyltransferase (peptidoglycan synthase) and the P-phospholipid carrier by binding to D-alanyl D-alanine. This prevents the synthesis and polymerization of NAM and NAG inside the peptidoglycan layer. With the weakening of bacterial cell walls brought on by this inhibition, intracellular components eventually seep out, leading to the death of the bacteria. Only gram-positive bacteria are susceptible to vancomycin.

Spectrum of Activity

Vancomycin is bactericidal for gram-positive bacteria in concentrations of 0.5–10 mcg/mL. Most pathogenic staphylococci, including those producing β lactamase and those resistant to nafcillin and methicillin, are killed by 2 mcg/mL or less. Vancomycin kills staphylococci relatively slowly and only if cells are actively dividing(24); the rate is less than that of the penicillins both in vitro and in vivo. Vancomycin is synergistic in vitro with gentamicin and streptomycin against Enterococcus faecium and Enterococcus faecalis strains that do not exhibit high levels of aminoglycoside resistance.

Antimicrobial spectrum includes Staphylococcus aureus (vancomycin susceptible), Coagulase negative Staphylococci, Streptococcus pneumoniae, Streptococcus spp., Enterococcus spp. (Vancomycin-susceptible), C. jeikeium, Clostridium spp., L. monocytogenes, Actinomyces.(A)



3.3 MECHANISM OF RESISTANCE

echanism Of Resistance

sistance to vancomycin in enterococci is due to modification of the D-Ala-D-Ala binding site of the peptidoglycan ilding block in which the terminal D-Ala is replaced by D-lactate .This results in the loss of a critical hydrogen bond at facilitates high-affinity binding of vancomycin to its target and loss of activity.

his mechanism is also present in vancomycin-resistant S aureus strains (MIC ≥ 16 mcg/mL),(25) which have acquired e enterococcal resistance determinants. The underlying mechanism for reduced vancomycin susceptibility in

vancomycin-intermediate strains (MICs = 4–8 mcg/mL) of S aureus is not fully known.

However these strains have altered cell wall metabolism that results in a thickened cell wall with increased numbers of D-Ala-D-Ala residues, which serve as dead-end binding sites for vancomycin. Vancomycin is sequestered within the cell wall by these false targets and may be unable to reach its site of action.

Administration

The FDA has approved both intravenous injection and oral administration of vancomycin. Infections caused by Clostridium difficile can be treated with Rectal administration of vancomycin which is an off-label use of vancomycin.The type and location of the infection determine the administration technique(26). As vancomycin has low oral absorption, it is typically taken intravenously to treat infections.MRSA infections and other gram-positive organisms that are sensitive can be treated with intravenous vancomycin injection. It is offered as a 5 mg/mL IV solution, a 10 mg/mL NaCl 0.9% solution, a 5 mg/mL dextrose 5% solution, or a 10 mg/mL NaCl 0.9% solution.Moreover, it is offered in vials containing 500 mg, 1 g, 1.25 g, 1.5 g, and 10 g of sterile powder for reconstitution.

Pharmacodynamics/Kinetics

- Bacterial growth inhibition: slowly bactericidal
- Parameter for PK/PD: AUC: MIC
- Bioavailability: Less than 10% of oral vancomycin is available for absorption.
- Vancomycin has a quick onset of action, reaching its highest serum concentration right after the intravenous infusion is finished. At this time, it is unclear when oral vancomycin starts to work.
- Substantial volume of distribution (0.4 L/kg to 1.0 L/kg) was found in bodily tissues and fluids(27), but not in cerebrospinal fluid (CSF) or meninges that were inflamed.
- Binding to proteins: around 55%

- No clear evidence of metabolism (excreted unchanged)
- Clearance ranges from 0.71 mL/min/kg to 1.31 mL/min/kg in adults with healthy kidneys.
- Half-life: In healthy people with appropriate renal function, vancomycin has a terminal half-life of 4 to 6 hours and an initial half-life which is relatively short(28). Patients with renal impairment had considerably longer elimination half-lives. These patients require close observation.
- Excretion: The kidney's glomerular filtration system removes 75% of the intravenous vancomycin injection through urine. The majority of oral vancomycin excretion occurs in faeces.

Clinical Uses approved by FDA

- Oral delivery of Clostridium difficile-associated diarrhea
- Endocarditis caused by Diphtheroid, Enterococcal, Staphylococcal, and Streptococcal species. Staphylococcus enterocolitis. Pseudomembranous colitis.
- Staphylococcal infections
- Lower respiratory tract infections
- Septicemia,
- Skin and soft tissue infections

Unapproved Clinical Uses

- Infections brought on via catheters bacterial pneumonia acquired in the community and Clostridium difficile infection
- Bacterial meningitis, intra-abdominal infections caused by MRSA or ampicillin-resistant enterococci, bacterial endophthalmitis (systemic or intravitreal administration)(29), native vertebral osteomyelitis, peritonitis, and prosthetic joint infections are just a few examples of diseases that can be prevented in newborns
- Surgical site infections; surgical prophylaxis; necrotizing skin and soft tissue infections

Adverse Effects

Intravenous Vancomycin Injection

Nephrotoxicity, hypotension, and hypersensitivity reactions are typical side effects of intravenous vancomycin administration. Vancomycin can cause a specific kind of hypersensitivity reaction known as anaphylaxis. Rapid intravenous infusions of vancomycin are linked to Redman syndrome, an infusion-related response. Flushing, pruritus, and an erythematous rash on the face, neck, and upper chest are some symptoms(30). Red man syndrome symptoms may develop 4 to 10 minutes into or right after following an infusion. Red man syndrome affects individuals anywhere from 3.7% to 47% of the time.Yet, there is a direct link between higher rates of vancomycin administration and a rise in the prevalence of red man syndrome. Red man syndrome, which is accompanied by angioedema and hypotension, can result from a rapid infusion of vancomycin(31)..Thus, the main therapeutic technique utilised to alleviate red man syndrome is to extend the infusion period. Nonetheless, red man syndrome can be avoided with the help of premedication with antihistamines like diphenhydramine or hydroxyzine. Localized phlebitis, chills, drug fever, skin rash, eosinophilia, and reversible neutropenia are less frequent side effects. Patients have occasionally reported Stevens-Johnson syndrome, ototoxicity, thrombocytopenia, vasculitis, and DRESS syndrome (drug rash with eosinophilia and systemic symptoms)(32).

Oral vancomycin

Oral vancomycin frequently causes gastrointestinal side effects as nausea and abdominal pain. Moreover, a typical negative side effect specific to vancomycin oral solution is dysgeusia, or impaired sensation of taste.If these side effects are severe and troublesome, patients should visit a doctor. Keep in mind that many of these negative effects are transient(33).Peripheral oedema, lethargy, headaches, diarrhea, flatulence, vomiting, back pain, urinary tract

infections, and fever are less frequent side effects of oral vancomycin. There have been isolated reports of patients taking oral vancomycin developing interstitial nephritis, red man syndrome, nephrotoxicity, ototoxicity, thrombocytopenia, and vasculitis.

Contraindications

Those who have a history of known hypersensitivity to vancomycin or any ingredient in the formulation should not take it.

Pregnancy considerations

For use during pregnancy, oral vancomycin capsules are classified as a category B medication. In contrast, category C refers to intravenous vancomycin injection. Use of vancomycin during pregnancy is not advised unless the advantages outweigh the hazards(34).To lessen the chance of ototoxicity and nephrotoxicity in the foetus, frequent monitoring of maternal blood is advised if treatment with vancomycin is required. There is now no proof that maternal vancomycin use causes harm to the fetus, according to studies on animals.Vancomycin, however, crosses the placenta and has been found in cord blood, amniotic fluid, and foetal serum. If a woman becomes pregnant while taking vancomycin, she should call her doctor right away.

Also, it is important to remember that pregnant women may need higher doses of vancomycin due to changes in pharmacokinetics, such as a bigger volume of distribution and a higher total plasma clearance.

Renal impairment

Vancomycin may build up in the body as a result of the impaired renal function, raising the risk of side effects. Renal insufficiency necessitates dosage modifications.For all patients with renal impairment, close monitoring of vancomycin trough concentrations is essential(35).Vancomycin may exacerbate renal impairment, so patients should be advised to contact their doctor if they notice signs of diminished kidney function, such as decreased urine output, edema, or

stomach pain.

Drug Interactions

Vancomycin and other drugs co-administered together may raise the risk of side effects and toxicity. Hence, when combining vancomycin with specific drugs, dose changes, further monitoring, and evaluation of alternative treatment should deserve attention(36).Vancomycin should be used with caution when combined with other nephrotoxic medications such aminoglycosides, amphotericin derivatives, and Intravenous contrast.

Monitoring

The safety and effectiveness of the drug must be monitored in patients taking vancomycin therapy. Complete blood cell counts and periodic renal function tests can be used to evaluate how well the patient is responding to the medication(37)

When administering intravenous vancomycin injection to the following individuals, assessment of vancomycin trough concentrations is strongly recommended:

- An invasive or severe infection
- Critical illness
- Impaired or unstable renal function
- Morbid obesity (body mass index greater than or equal to 40 kg/m)
- Advanced age
- Inadequate response to therapy after three to five days
- Use of nephrotoxic substances concurrently (i.e., aminoglycosides, piperacillin-tazobactam, amphotericin B, yclosporine, loop diuretics, nonsteroidal anti-inflammatory drugs, contrast dye).

t is also advised to monitor vancomycin trough concentrations in stable patients with normal renal function to evaluate

whether the clinical response was adequate. Healthcare providers can evaluate the efficacy of the vancomycin dosing schedule and the patient's individual drug clearance by obtaining vancomycin serum trough concentrations.(38) Depending on the indication, the target therapeutic serum trough concentration typically ranges between 10 and 20 mcg/mL.

Ideally, serum trough concentrations should be measured as soon as possible (30 minutes or fewer) before a dose is given under steady-state conditions. Usually, steady-state occurs following the third vancomycin dose.Due to a lack of systemic absorption, oral vancomycin normally does not need serum concentration monitoring, unlike intravenous vancomycin injection.

Toxicity

Nephrotoxicity and ototoxicity have correlations with the use of vancomycin

Although there are numerous case reports of acute renal failure attributed to vancomycin use, there is currently limited data suggesting a direct causal relationship Vancomycin's oxidative action on cells in the proximal renal tubule is thought to be the cause of renal tubular ischemia, which is the suggested mechanism of nephrotoxicity(39).Preexisting renal impairment, concurrent use of nephrotoxic medicines, advanced age, and dehydration are typical risk factors for nephrotoxicity. Although though vancomycin-induced nephrotoxicity is frequently treatable, it might be difficult to distinguish it from acute interstitial nephritis and deteriorating renal function brought on by uncontrolled infection. In the absence of a causal explanation, elevations in serum creatinine are indicative of vancomycin-induced nephrotoxicity(40). One popular technique for avoiding nephrotoxicity is to dose vancomycin depending on predicted creatinine clearance. Patients who experience signs of acute renal failure precipitated by vancomycin use should promptly discontinue their therapy. It's also vital to remember that both oral and intravenous vancomycin use have been associated to incidences of nephrotoxicity. Vancomycin nephrotoxicity cases have typically included patients over the age of 65.

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),(41) and those with underlying hearing loss conditions. Patients should discontinue receiving treatment if they exhibit symptoms of ototoxicity such tinnitus, hearing loss, and unsteady movements. It merits noting that vancomycin-induced ototoxicity may be irreversible. Testing for auditory function may help to identify early symptoms(42).

Need for the study

The need for antibiotic therapy is seemingly increasing everyday, and vancomycin being a reserved drug is given to patients to counter a narrow variety of infections. Even though Vancomycin has many side effects its more often prescribed to patients as it reduces hospital stay. It is very important to monitor the dosage form, the frequency , time of administration and related adverse effects. This prospective study aims to identify the adverse reactions caused due to Vancomycin therapy and discuss methods to counteract the same. No such studies have been conducted in India and hence this study highlights the importance of why it should be carried out .

AIM AND OBJECTIVES

AIM

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1. To analyze the safety of vancomycin in hospitalized patients
2. To analyze the clinical outcomes of vancomycin.
3. To document the duration , dose of vancomycin therapy and adverse effects if any.
4. To propose standard treatment guidelines of vancomycin therapy in hospital under the consultation with nephrology department.