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A REVIEW ON THE USE OF VANCOMYCIN

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ABSTRACT

Vancomycin has concerns about nephrotoxicity since its approval in 1958. First preparations were named "Mississippi mud" and had notable impurities are the considerable reason for the nephrotoxicity. Through improved procedures, present preparations contain ~90–95% vancomycin B (the active moiety). The rate of nephrotoxicity with use of modern preparations varies in the literature, with the occurance ranging from as low as 0% in the absence of concurrent nephrotoxins to over 40%. It is widely used in hospitals, indicated to fight serious infections caused by Gram-positive bacteria, mostly with the occurance of MRSA (methicillin-resistant Staphylococcus aureus), penicillin-resistant pneumococci among others. Additionally, it is used for the treatment of patients allergic to penicillins and cephalosporins. Dose recommendations, dilution rates and types of infusion are difficult and also result in toxic effects. The important adverse effects of vancomycin are: hypotension, phlebitis, nephrotoxicity, ototoxicity, hypersensitivity reactions, red man syndrome, neutropenia, chills, fever, interstitial nephritis. The use of vancomycin is still very common; however, inappropriate doses and long term therapy cause the risk of increasing minimum inhibitory concentrations (MICs), resulting in subtherapeutic levels, treatment failures and toxicity. Therefore, improve in administration of vancomycin, monitoring treatments from the beginning in order to make sure a safe and effective use of the drug.

KEYWORDS: Vancomycin, Toxicity, Adverse effect.

INTRODUCTION

Vancomycin is a complex tricyclic glycopeptide antibiotic produced by Streptococcus orientalis.[1,2] Vancomycin is absorbed very small amount by the gastrointestinal tract; thus, it is administered intravenously and its mechanism of action is the inhibition of the bacterial cell wall biosynthesis or, the inhibition of peptidoglycan biosynthesis.[4] Therefore, bactericidal for reproductive bacteria.[1] Vancomycin is generally used for serious infections caused by Gram-positive bacteria, and microorganisms that are resistant to other antimicrobial agents or patients who are allergic to penicillins and cephalosporins.[1,5] It is widely used in intensive care units (ICU) for the treatment of hospital infections and sepsis, pneumonia cases, endocarditis, osteomyelitis, soft tissue abscesses.[1,6,7] This drug is not a first-choice due to its adverse effects like hypotension and tachycardia, phlebitis, nephrotoxicity, ototoxicity,[7] hypersensitivity reactions, chills, exanthema and fever,[1] and the peripheral IV complications are a major hazard.[8] The use of wrong doses and extended therapies increase the risk of toxicity which, causes the adverse effects.[1,4,9,10-14] Some studies shows that the major important adverse effects are nephrotoxicity and ototoxicity.[15-17]

General aspects

Vancomycin is a complex tricyclic glycopeptide antibiotic, produced by Streptococcus orientalis, which has been used for approximately 50 years.[1,2] Its molecular weight is 1,500 daltons.[1]

Absorption, Distribution, Excretion

As vancomycin is absorbed very small amount by the gastrointestinal tract; so, it is administered intravenously. Intravenous administration of 1g of vancomycin produces15 to 30 µg/ml/ hour plasma concentration after 1-2-hour of infusion.[1] The redistribution of vancomycin makes the analysis of peak plasma concentration of the drug more difficult, as there is a variation according to the individual's age.[3] It is eliminated by renal excretion, and only 5% of the drug is metabolized.[3,18] Approximately 90% of the administered drug is excreted by glomerular filtration.[1] Its plasma half-life ranges from 4 to 11 hours, average of 6 hours in patients with normal renal function. In case of renal failure, the half-life is around 7 days.[3]

Mechanism of action

The mechanism of action of vancomycin is the inhibition of the bacterial cell wall biosynthesis or, inhibition of peptidoglycan biosynthesis. Therefore, bactericidal for

reproductive bacteria.[1] The bacterial cell wall contains peptidoglycan that enclose the bacteria.[4] In Gram-positive bacteria this substance is high, and it forms large and insoluble layers on the outer part of the cell membrane, up to 40 layers which consist of amino sugars: N-acetylglucosamine and N-acetylmuramic.[4] The latter contains peptide residues with cross-links, which form a resistant polymeric chain.[4] The drug inhibits this polymerization, once it binds with high affinity to the C-terminal D-alanyl D-alanine residues of lipid-linked cell wall precursors and blocks the linkage to the glycopeptide polymer.[1] As a result, it block the cross-links of peptides from binding to tetrapeptide side chains, it block its linkage to peptidoglycan.[4]

Antibacterial activity

Vancomycin is used to fight Gram-positive bacteria. The strains are sensitive when the minimum inhibitory concentration is $\leq$ 4 µg/ml.[1] it is effective against Staphylococcus aureus, S. epidermidis, S. pyogenes, S. pneumoniae, streptococcus viridans and species of Bacillus, Actinomyces, Clostridium and Corynebacterium.[1] Also, a huge part of Gram-negative bacilli, mycobacteria and fungi are resistant to vancomycin.[1,3] This antibiotic has become even more applicable with the occurance of MRSA (methicillin-resistant Staphylococcus aureus)[24] and penicillin-resistant pneumococcal infections[1]also other bacterial resistance mechanisms against beta-lactam antibiotics.[2]

Therapeutic use

Vancomycin is intravenously administered in hospitals, and it is available in sterile powder form for dilution.[1,18] Guidelines suggested a dilution of 2.5 to 5.0 mg/Ml.[3] The dose for adults is 30 mg/kg/day fractioned in 2 or 3 doses; but, higher doses may be prescribed[1]. However the peadiatric doses vary according to the age range given below.[1,3]

- 15 mg/kg in the beginning, followed by 10 mg/kg every 12 hours for newborns (first week of life).[1]
- 15 mg/kg, followed by 10 mg/kg every 8 hours for newborns from 8 to 30 days of age.[1]
- 10 mg/kg every 6 hours for infants and older children.[1]
- Children with bacterial endocarditis: 20 mg/kg administered over 1 to 2 hours. Infusion must be interrupted 30 minutes prior to the beginning of the surgery.[3]

Standard doses as well as infusion dilution, rate and type are still difficult, and less knowledge about the pharmacological effects or safety of this drug in pediatric patients, mainly in newborns.[18-22] This medication is used with caution in patients with impaired renal

function. Doses should be adjusted and such patients must be monitored, so, minimizing the risks of nephrotoxicity and ototoxicity.[3]

Efficacy and Toxicity

In 2009 an International Consensus Guidelines, point to develop the administration and therapeutic monitoring of vancomycin, was published and it is still unanswered questions. Although, for all the general review and awareness of increased MICs, treatment failures and toxicity, vancomycin is widely used in health centers.[20] Other studies suggest that the vancomycin used only to start the antimicrobial therapy and that there is no ideal standard dose.[7,26] Also, Giachetto et al[27] point up variations in pharmacokinetics parameters in children in critical condition. Therefore, therapeutic monitoring, dosage individualization, the ideal doses and the evaluation of the renal function are very important to be taken from the beginning of the treatment, so that the administration of vancomycin can be safe and effective.[1,3,9,10-14]

Adverse effects of vancomycin

Nephrotoxicity and ototoxicity have basically been recorded as rare complications of vancomycin monotherapy. Present-day reports have linked aggressive vancomycin dosing strategies to remarkable risks of nephrotoxicity.

Vancomycin is not a first choice due to its adverse effects, like hypotension and tachycardia, phlebitis, nephrotoxicity, ototoxicity,[5] hypersensitivity reactions, chills, exanthema and fever,[1] but also to a major concern on peripheral IV complications.[8] Besides, international consensus guidelines for the rational use of vancomycin are still difficult and very little is known on the safety of this drug.[18-22] Thus, the literature given the use of insufficient doses and long term therapy, increasing the risks of toxic levels and the onset and worsening of adverse effects.[1,3,9-14] The main adverse effects of vancomycin are given below.

Drug interactions

Vancomycin isn't right for everyone. Determined by what other drugs you take, you might experience a drug interaction. Several drug interactions with vancomycin are mild to minor and should be monitored by a physician if taking them together. For example, vancomycin can be vigorous on your kidneys. If you are taking other antibiotics that can also cause kidney damage, such as cidofovir, you'll want to regularly check in with your doctor to stop any significant damage.

Vancomycin, like other antibiotics, also reduces the effectiveness of estrogen-based contraception. It can also decrease the efficacy of certain live vaccines, like typhoid. This is incredibly important if your patient is traveling to an area with active typhoid cases, wait until the live vaccine has produced full immunity before continuing with vancomycin treatment. Some drugs, like aspirin or naproxen can affect even kidneys are working. These drugs are routinely prescribed for inflammatory pain. Since vancomycin is eliminated through the kidneys, if taken with these medications, it is not removed from the body as well. This leads to higher concentrations of vancomycin in the blood than expected. This is a minor drug interaction, and should just be monitored by a physician.

Bacterial resistance

Vancomycin resistance is generated by a change in peptidoglycan terminal, developing in decreased vancomycin binding and failure to stop cell wall synthesis. Resistance in vancomycin-intermediate S. aureus and glycopeptide-intermediate S. aureus may be because of the making of unusual peptides ("false binding sites") in the cell wall that bind vancomycin and stop its bond to its receptor or may be to a growth of peptidoglycan arising in thickened cell walls. A form of resistance is seen in S. pneumoniae by a individual mutation in the sensor-response system that controls autolysin activity required to kill certain bacteria.

Ototoxicity

Ototoxicity is a rarely reported adverse effect of vancomycin and has not been as quickly revealed, although vestibular damage and/or cochlear damage related with tinnitus and sensorineural hearing loss has been described in humans after administration of vancomycin. Ototoxicity may be a temporary or permanent side effect of vancomycin therapy and is associated to elevated serum levels. Symptoms usually sort out after reducing the dose or termination of vancomycin. In the case of low risk of vancomycin ototoxicity, it is suggested to stop vancomycin in patients undergoing signs of ototoxicity including tinnitus, loss of balance or loss of hearing.

The literature disclose a considerable amount of cases of hearing loss related with the use of vancomycin. The mechanism is based on the direct damages caused by the drug to the auditory branch of the eighth cranial nerve. In some cases the damage is irreversible, and this is due to the high drug concentrations in the plasma (60 to 100 µ/ml). In many cases, patients already have renal dysfunction or hearing loss, and they were under treatment with other

ototoxic drug.[1,29,30] Therefore, the use of vancomycin should be avoided in patients with hearing loss. Vertigo, dizziness and tinnitus are side effects that have rarely been reported, but tinnitus may be a symptom before the hearing loss which order the rapid termination of the drug administration.[1,29,30]

Nephrotoxicity

Vancomycin use is often associated with nephrotoxicity. It remains unknown, although, to what proportions vancomycin is directly responsible, as variuos potential hazard for acute kidney injury regularly coexist.

The percentage of the cardiac output of the kidneys is approximately 20-25%. This is 1.100 ml/min, which is required for the regulation of body fluids and solutes.[31] Vancomycin are widely known as toxic substances, normally patients with severe diseases or those who present hypersensitivity reaction to beta-lactam antibiotics are allowed to therapy with this class of drugs.[40] The first reported cases of vancomycin nephrotoxicity were related with the impurities found in the drug. With the improvement of the production and removal of impurities from drugs, renal lesions have been aspect to other mechanisms.[41] But such mechanisms of action are not clearly known, studies show that nephrotoxicity is present in 7-17% of patients who use the drug intravenously in the treatment of infections by methicillin-resistant Staphylococcus aureus (MRSA).[40]

Studies shows that acute interstitial nephritis (AIN) is the main mechanism of vancomycin-induced nephrotoxicity. It is crucial to identify the renal injury in such cases once the renal function isgetbetter when the use of the medication is stopped. But, if administration is continued, the kidneys are highly affected with possible irreversible damage, mainly in the elderly population.[30,35] It is important to highlight that the increase in cases of vancomycin-resistant MRSA makes clinicians to prescribe vancomycin dosing (15-20 mg/ml). High doses of the drug are related with a high risk of nephrotoxicity. But, in many cases, this is related to long or periodic treatments, to patients who received related therapy with aminoglycosides, or yet, to those with renal dysfunction.[30,42]

Therapeutic drug monitoring

Plasma level monitoring of vancomycin is mandatory due to the drug's biexponential distribution, intermediate hydrophilicity, and potential for ototoxicity and nephrotoxicity, mainly in people with poor renal function and/or elevated tendency to bacterial infection. Its

activity is examine to be time-dependent, hang on the period that the serum drug concentration exceeds the minimum inhibitory concentration of the target organism. Thus, peak serum levels have not been shown to relate with efficacy or toxicity; in fact, concentration monitoring is irrelevant in many cases. Circumstances in which therapeutic drug monitoring is warranted in patients receiving concomitant aminoglycoside therapy, patients with (potentially) altered pharmacokinetic parameters, patients on haemodialysis, patients administered high-dose or prolonged treatment, and patients with impaired renal function. In such cases, trough concentrations are measured. Firing ranges for serum vancomycin concentrations have replaced over the years. Peak levels of 30 to 40 mg/L and trough levels of 5 to 10 mg/L, but present advices are that peak levels not required to be estimated 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 certain needs of the patient, may be relevant. Using estimated vancomycin concentrations to calculate doses perfect therapy in patients with augmented renal clearance.[43-44]

CONCLUSION

Vancomycin has been useful for the past 50 years and still widely administered in hospitals. Although, no matter how long this drug has been clinically used, dose recommendations, dilutions, monitoring, infusion types and rates are still difficult. These factors indicate that the adverse effects related to the use of vancomycin. Therefore, there is a require to updated information about the pharmacology and the safety. The initiation of ideal doses, dilutions, infusion types and rates, therapeutic and clinical monitoring as well as the evaluation of the renal function are important from the beginning of the treatment so that there is a safe and individualized administration of the drug can be possible. Otherwise, the use of inappropriate doses and long-term therapies increase the risks of toxicity and the onset of adverse effects.

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