European Review for Medical and Pharmacological Sciences 2015; 19: 694-700

The use of vancomycin with its therapeutic and adverse effects: a review

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Abstract. – OBJECTIVE: Vancomycin (VCM) is a tricyclic glycopeptide antibiotic produced by *Streptococcus orientalis*. Widely used in hospitals, it is indicated to fight severe infections caused by Gram-positive bacteria, especially with the advent of MRSA (methicillin-resistant *Staphylococcus aureus*), penicillin-resistant pneumococci among others. Furthermore, it is indicated for the treatment of patients allergic to penicillins and cephalosporins. Dose recommendations, dilution rates and types of infusion are controversial and also result in toxic effects. Aim of this paper was to perform a literature review showing the therapeutic and adverse effects of vancomycin.

MATERIALS AND METHODS: This is a literature review of recent articles published on MEDLINE and SciELO databases in English, Portuguese and Spanish.

RESULTS: The main adverse effects of vancomycin are: hypotension, phlebitis, nephrotoxicity, ototoxicity, hypersensitivity reactions, red man syndrome, neutropenia, chills, fever, interstitial nephritis.

CONCLUSIONS: The use of vancomycin is still very common; however, inadequate doses and prolonged therapy pose a risk of increasing minimum inhibitory concentrations (MICs), resulting in subtherapeutic levels, treatment failures and toxicity. Therefore, further studies should be conducted to optimize the administration of vancomycin, monitoring treatments from the beginning in order to ensure a safe and effective use of the drug.

Key Words:
Vancomycin, Toxicity, Endothelial injury, Oxidative stress.

Introduction

Vancomycin is a complex tricyclic glycopeptide antibiotic produced by *Streptococcus orientalis*[1,2].

As this drug is very little absorbed by the gastrointestinal tract; it is, thus, intravenously administered[3] and its mechanism of action is the inhibition of the bacterial cell wall biosynthesis or, in other words, the inhibition of peptidoglycan biosynthesis[4]. It is, therefore, bactericidal for reproductive bacteria[1].

VCM is generally prescribed to combat severe infections caused by Gram-positive bacteria, to fight microorganisms that are resistant to other antimicrobial agents or still indicated to patients who are allergic to penicillins and cephalosporins[1,5]. As a consequence, it is very much used in intensive care units (ICU) for the treatment of not only hospital infections and sepsis, but also of pneumonia cases, empyema, endocarditis, osteomyelitis, soft tissue abscesses among others[1,6,7].

This drug is not the first-choice agent owing to its adverse effects like hypotension and tachycardia, phlebitis, nephrotoxicity, ototoxicity[7], hypersensibility reactions, chills, exanthema and fever[1], and the fact that peripheral IV complications are a major concern[8]. The literature reveals that the use of inappropriate doses and prolonged therapies increase the risk of toxicity which, in turn, favors the onset of adverse effects[1,4,9,10-14].

Some experimental studies show the induction of oxidative stress through the increase of reactive oxygen species (ROS) generation as important adverse effects like nephrotoxicity and phlebitis[15-17]. Moreover, the literature is very controversial regarding recommended doses, dilution rates and types of infusion, which indicate how little is known about this antibiotic in terms of pharmacology and safety, particularly its effects in newborns and children[18-22].

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The aim of this study is to perform a review on the adverse effects of vancomycin, which can help health professionals rethink the current available protocols and minimize such effects.

Materials and Methods

Articles on vancomycin and its adverse effects, published on MEDLINE and SciELO databases in English, Portuguese and Spanish, have thoroughly been studied, revised and updated.

General Aspects

Vancomycin is an unusual complex tricyclic glycopeptide antibiotic, produced by *Streptococcus orientalis*, which has usefully been employed for approximately 50 years[1,2]. Its molecular weight is 1,500 daltons[1], and its structural formula is shown in Figure 1.

Absorption, Distribution and Excretion

As vancomycin is little absorbed by the gastrointestinal tract, it is thus intravenously administered[3]. In adults, a single intravenous dose of 1 g produces plasma concentrations of 15 to 30 µg/ml 1 hour after a 1- to 2-hour infusion[1].

The redistribution phenomenon in vancomycin concentrations makes the analysis of peak plasma concentration of the drug more difficult, as there is a variation according to the individual's age[3]. The medication is eliminated by renal excretion, and only 5% of the drug is metabolized[3,18]. Around 90% of the administered dose is excreted by glomerular filtration[1]. Its plasmatic half-life ranges from 4 to 11 hours, with an average of 6 hours in patients with normal renal function. In case of renal failure, the half-life is approximately 7 days[3].

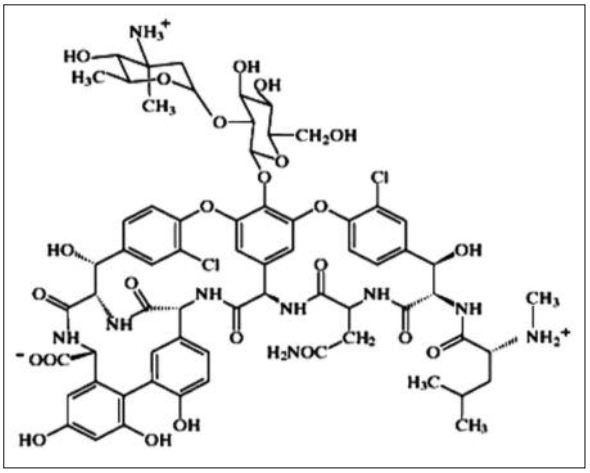

Figure 1. Structural formula of vancomycin[23].

Mechanism of Action

The mechanism of action of this antimicrobial agent is via the inhibition of bacterial cell wall biosynthesis or, more specifically, the inhibition of peptidoglycan biosynthesis. It is, therefore, bactericidal for reproductive bacteria[1].

The bacterial cell wall contains peptidoglycan that encircles the whole bacteria[4]. In Gram-positive bacteria this substance is more significantly present, and it forms large and insoluble layers on the outer part of the cell membrane, totaling up to 40 layers which consist of multiple skeletons of amino sugars: N-acetylglucosamine and N-acetylmuramic[4]. The latter contains lateral short peptide residues with cross-links, which form a high-level resistant polymeric chain[4]. The drug inhibits this polymerization or the transglycosylase reaction 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 hinders the cross-links of peptides from binding to tetrapeptide side chains, namely, it prevents its linkage to the growing tip of the peptidoglycan[4].

Antibacterial Activity

Vancomycin is especially prescribed to fight Gram-positive bacteria. The strains are considered sensitive if the minimum inhibitory concentration is ≤ 4 µg/ml[1].

In general it is effective against *Staphylococcus aureus*, S. *epidermidis*, S. *pyogenes*, S. *pneumoniae*, *streptococcus viridans* and species of *Bacillus*, *Actinomyces*, *Clostridium* and *Corynebacterium*[1]. On the other hand, a great part of Gram-negative bacilli, mycobacteria and fungi are resistant to vancomycin[1,3].

This antibiotic has become even more relevant with the advent of MRSA (methicillin-resistant *Staphylococcus aureus*)[24] and penicillin-resistant pneumococcal infections[1] besides other bacterial resistance mechanisms against beta-lactam antibiotics[2].

Therapeutic Use

On the whole vancomycin hydrochloride is intravenously administered in hospitals, and it is commercially available in sterile powder form for dilution[1,18]. Guidelines recommend a dilution of 2.5 to 5.0 mg/mL[3].

The usual dose for adults is 30 mg/kg/day fractioned in 2 or 3 doses; however, higher doses may be prescribed[1]. Although the established pediatric doses vary according to the age range described below[1,3], no consensus has been reached regarding the adequate dose of vancomycin for children.

- 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 (continuous or intermittent deliveries) are still controversial, and very little is known about the pharmacological effects or safety of this drug in pediatric patients, especially in newborns[18-22].

This medication must be used with extreme caution in patients with impaired renal function. Doses should be adjusted and such patients must be monitored, thus, minimizing the risks of nephrotoxicity, ototoxicity among others[3].

Posology, Efficacy and Toxicity

In 2009 an International Consensus Guidelines, aiming to optimize the administration and therapeutic monitoring of vancomycin, was published and it raised still unanswered questions. However, despite the general concern and perception of increased MICs, treatment failures and its toxicity, vancomycin has been widely used in many health centers[20].

Some studies show that the recommended doses established in published guidelines are not always adequate since they do not reach therapeutic serum levels in a timely manner in patients with normal renal function[9,25]. Other recent studies suggest that the recommended vancomycin doses should be used only to start the antimicrobial therapy and that there is no ideal standard dose[7,26]. On the other hand, Giachetto et al[27] highlight alterations in pharmacokinetics parameters in children in critical condition.

Therefore, therapeutic monitoring, dosage individualization, the establishment of ideal doses and the evaluation of the renal function are paramount actions to be taken from the beginning of the treatment with vancomycin so that the drug administration can be safe and effective, especially in children and newborns[1,3,9,10-14]. Contrarily, the use of inadequate doses and the prolonged therapy increase the risks of subtherapeutic and toxic levels of the drug which favor the development of resistant microorganisms and the onset of adverse effects[1,3,7,9-14,26,27].

Adverse Effects of Vancomycin

Vancomycin is not an agent of first choice owing not only 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, like mentioned before, international consensus guidelines for the rational use of vancomycin are still controversial and very little is known on the safety of this drug[18-22]. As a result, the literature establishes the use of inadequate doses and prolonged 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 described below.

Hypersensitivity Reaction

Antimicrobials and anticonvulsants are the drugs more commonly associated with hypersensitivity reactions. However, all drugs are potentially able to cause such effects[28].

These reactions may be triggered by immune or non-immune mechanisms, and cutaneous manifestations stand as one of the major alterations. They are classified as severe when cutaneous lesions are extensive or when they affect multiple organs. Drug hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute exanthematic pustulosis figure among the most severe causes[28].

Urticaria, exfoliative dermatitis, macular rashes, eosinophilia, vasculitis, transient anaphylaxis, and, occasionally, vascular collapse have been reported as vancomycin-induced reactions. The drug has also been associated with Stevens-Johnson syndrome in at least one patient[29,30].

Nevertheless, the most common manifestations are macular cutaneous rashes and anaphylaxis, including hypotension, dyspnea, urticaria or itching[1,30].

Cutaneous rashes, like maculopapular exanthema, are characterized by itchy or non-itchy spreading lesions that may start on the trunk and upper limbs. Such rashes tend to disappear within 7 to 10 days after medication suspension[28].

Urticaria generally occurs within 7 to 14 days after exposition to the drug. It is characterized by short-lasting erythematous urtical lesions. However, the deep dermis and subcutaneous tissues may be affected in some cases, and in severe cases, they are associated with anaphylaxis[28].

Overall, anaphylaxis caused by drugs is responsible for around 13-20% of the total cases[28]. It is a potentially severe case triggered by immunoglobulin-E (IgE) mediated reactions, characterizing the type-1 hypersensitivity mechanism. It is an allergic condition in which the cardiac output and blood pressure levels are altered[31]. The major effect is related to the histamine and other inflammatory mediators released by basophils and mastocytes, causing vasodilatation, bronchoconstriction, capillary permeability increase, autonomic nervous system activation and mucosal hypersecretion. Therefore, it is necessary to be aware of the most severe cases, like hypotension, bronchial spasms or laryngeal edema[31].

Events Related to Infusion

The drug must be slowly infused, at a maximum rate of 10 mg/minute, over a period of at least 60 minutes, with rotation of venous access sites[3,5]. Adverse effects are, therefore, avoided since fast IV infusion may cause pain, phlebitis, erythema, urticaria, flushing, hypotension, tachycardia and the red man syndrome[1,5,32].

The red man syndrome is characterized by the onset of intense redness over the upper part of the body ("red neck") or painful trunk muscle spasms. These reactions generally disappear within 20 minutes, but they may linger for many hours. It is a common yet unpredictable situation that occurs owing to a direct toxic effect of vancomycin over mastocytes, releasing histamine[1,32]. In this case, there may occur a sudden drop in blood pressure followed by dyspnea, angioedema, urticaria and pruritus. The physiopathology is related to the negative inotropic effect and the vasodilator action stimulated by the histamine release. In acute cases the use of antihistamines, corticosteroids or IV fluids may be required[29,30].

An experimental study performed in 2010[33] reveals that the drug may also directly influence on the vascular tonus, affecting the microcirculation during endotoxemia and sepsis in rats. Moreover, another study corroborates these findings[8] when it reports that patients receiving vancomycin are more likely to present greater peripheral IV complications when compared with patients under the administration of other types of antibiotics.

It is important to point out that vancomycin is irritating to tissue, and it must be given by a secure intravenous route of administration. Pain, tenderness and necrosis occur with inadvertent extravasation[1,30].

Thrombophlebitis, which may be associated with chills, exanthema and fever, is also an event related to infusion. However, occurrence frequency and severity many be minimized, like mentioned before, by slowing the infusion rate of the drug and by performing the rotation of venous access sites[1,30].

Ototoxicity

The literature reveals a great amount of cases of hearing loss associated 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 there is a direct relation to the high drug concentrations in the plasma (60 to 100 μ/ml). In most cases, however, patients already presented renal dysfunction or pre-existing hearing loss, or even, they were under treatment with other ototoxic drugs[1,29,30].

Therefore, the use of vancomycin should be avoided in patients with previously diagnosed hearing loss. Vertigo, dizziness and tinnitus are side effects that have seldom been reported, but tinnitus may be a symptom before the onset of hearing loss which demands the immediate interruption of the drug administration[1,29,30].

Alterations in Free Radical Balance

Such balance alterations may be explained by an imbalance between the generation and elimination of free radicals. Oxidative stress is defined as a tissue damage caused by the imbalance between pro- and antioxidant factors. This fact, in turn, is associated with cell injury by lipid peroxidation, oxidative damage of proteins and DNA lesions[34,35].

Endothelial cells are important modulators of normal hemostasis. The perfect balance between anti- and prothrombotic activities of the endothelium determines whether thrombus formation, propagation or dissolution occurs[34]. One of the

major effects of oxidative stress is the impairment of biological activity of NO and the resultant endothelial dysfunction[35].

Some experimental studies in animals show the induction of oxidative stress by increase in the production of reactive oxygen species (ROS)[15,16] and expression changes of many complement system transcripts and of the inflammatory pathways with the use of vancomycin. Such events are responsible for some of the adverse effects of the drug, like nephrotoxicity, phlebitis and local pain[17,36].

A literature review published in 2012 reports renal toxicity associated with the use of vancomycin in 10-20% and 30-40% of the cases in conventional and high doses respectively. Elyasi et al[37] concluded that the probable mechanism for such injury is related to the induction of oxidative stress by increase in the production of ROS.

A study by Robibaro et al[38] not only reveals endothelial dysfunction with the use of vancomycin but also states that high concentrations of the drug lead to considerable damages in endothelial cells. These results may explain the common collateral effects associated with glycopeptides, like phlebitis and infusion site pain.

In another 2012 study performed with Wistar rats, researchers report[39] that thymoquinone, the tested substance, not only produces a protective mechanism against the nephrotoxicity induced by vancomycin but also suggests the important role played by the VCM in the oxidative stress induction.

Nephrotoxicity

The percentage of the cardiac output delivered to the kidneys is approximately 20-25%. This corresponds to 1.100 ml/min, allowing a high rate of glomerular filtration which is necessary for the regulation of body fluid volumes and the concentrations of solutes[31].

Kidney diseases, classified as severe or mild, are among the major causes of death and incapacitation in many countries. Many of their severe forms, which are able to affect blood vessels, glomeruli, tubules and the renal interstitium, may lead to renal insufficiency, the term that is used to define kidney malfunctions[31].

Glycopeptide antibiotics like vancomycin are widely known as toxic substances, and therefore indications for their use should be very precise – normally patients with severe diseases or those who present hypersensitivity reaction to beta-lactam antibiotics are eligible to therapy with this class of drugs[40]. Previously, the first reported cases of vancomycin nephrotoxicity were associated with the impurities found in the production of the drug. With the improvement of the production process and the gradual removal of impurities from drugs, renal lesions have been attributed to other mechanisms[41]. Despite the fact 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].

The available clinical laboratory exams can only show renal injuries caused by the use of vancomycin when nearly 50% of the total renal tissue is affected. Therefore, studies firstly try to elucidate the physiopathology, and some laboratories invest in the discovery of early ways to identify secondary kidney disorders as a result of medication therapies[40].

Some studies suggest that acute interstitial nephritis (AIN) is the main mechanism of vancomycin-induced nephrotoxicity. In this case, there is an immunological reaction with the presence of diffuse edema and inflammatory infiltrate in the interstitium, which is composed of mononuclear cells, mainly T-lymphocytes and macrophages. In some cases, plasmocytes and basophiles can be found, and eosinophils and neutrophils are commonly present. Some systemic alterations like fever, eosinophilia and exanthema can also be observed in selected cases of AIN. It is important to identify the renal injury in such cases once the renal function is recovered when the use of the medication is discontinued. However, if administration is maintained, the kidneys are highly affected with possible irreversible damage, especially in the elderly population[30,34].

In a study with animal models, Dieterich et al[40] used a genomic analysis to try to elucidate renal transcriptional responses after the use of vancomycin. The main conclusions from the experiments were: whenever the drug is administered in high doses, it accumulates in proximal tubular cells which, in turn, undergo the process of necrosis; the participation of oxidative stress, like mentioned before, as well as mitochondrial damage in vancomycin-induced renal injury were evident; some previously known gene expression markers to detect toxicity were dramatically altered when the antibiotic was present in high doses; last and most important, a potential participation of the complement system and of inflammatory mediators in the nephrotoxicity was identified.

Shah-Khan et al[41] have reported a case of acute tubular necrosis (ATN) as an isolated etiological factor of nephrotoxicity in a young female patient treated with vancomycin.

It is important to highlight the fact that the increase in cases of vancomycin-resistant MRSA makes clinicians gradually increase vancomycin dosing (15-20 mg/ml). High doses of the drug are associated with a high risk of nephrotoxicity. However, in most cases, this fact is related to prolonged or recurrent treatments, to patients who received concomitant therapy with aminoglycosides, or yet, to those with pre-existing renal dysfunction[30,42].

Others

It is important to mention some minor adverse effects of vancomycin: reversible neutropenia, thrombocytopenia; reversible agranulocytosis; gastrointestinal symptoms; pseudomembranous colitis[29,30].

Conclusions

Vancomycin is an antibiotic that has been useful for the past 50 years and it is still widely administered in hospitals. However, no matter how long this drug has been clinically used, dose recommendations, dilutions, monitoring, infusion types and rates are still controversial. All these factors contribute to the onset of adverse effects related to the use of vancomycin. Therefore, there is a lot yet to be learned about the pharmacology and, above all, the safety of this antibiotic.

As a result, the establishment of ideal doses, dilutions, infusion types and rates, therapeutic and clinical monitoring as well as the evaluation of the renal function are essential from the beginning of the treatment so that there can be a safe and individualized administration of the drug. On the other hand, the use of inadequate doses and prolonged therapies increase the risks of toxicity and the onset of adverse effects.

In the light of this fact, new double-blind randomized prospective studies should be conducted to establish how safe vancomycin really is.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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