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Review

Vancomycin as a risk factor for anaphylactoid reaction (Red Man Syndrome): Literature review

Rosa Eugenia Reyes R[1,2], Miguel Ángel Becerril G[3], Ma. Cristina Fresan O[2], Guadalupe A. Camacho V[4], Adrián de Jesús Guillé P[4] and Ma. Gabriela Pérez G[4*]

[1]Farmacia Hospitalaria, Instituto Nacional de Pediatría, CP 04530, Mexico City, México.
[2]Departamento de Sistemas Biológicos, División CBS. Universidad Autónoma Metropolitana Unidad Xochimilco, Cp. 04960, Mexico City, México.
[3]Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Unidad de Desarrollo e Investigación en Bioprocesos. Prolongación de Carpio y Plan de Ayala S/N, Col Santo Tomas. Cp 11340, Mexico City, México.
[4]Laboratorio de Farmacología, Instituto Nacional de Pediatría, CP 04530, Mexico City, México.

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Vancomycin is the antibiotic of first choice for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infection. Its use is associated with adverse effects in children with a frequency of 5 - 14% and in adults with 1.6 - 35%. Of these adverse effects to vancomycin, two kinds have been described. The first is anaphylactic immunologic or immediate hypersensitivity mediated by immunoglobulin type E (IgE). The second is IgE independent anaphylactoid reaction, also referred to as nonallergic drug hypersensitivities or pseudoallergic reactions, known as red man syndrome (RMS). The signs and symptoms of anaphylactoid reaction principally occur in the first dose of vancomycin and could be accompanied by hypotension and cardiac arrest. The severity of the reaction is proportional to the dose administered, infusion velocity, and liberation of histamine in blood.

Key words: Vancomycin, adverse effects, hypersensitivity, red man syndrome, histamine, infant population.

INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) is a public health problem. In U.S.A., the incidence of infection by MRSA in 2005 was estimated to be 31.8 per 100,000 inhabitants with mortality rate of 6.3/100,000 inhabitants (Svetitsky et al., 2009). Vancomycin is the drug of choice for the treatment of MRSA, *Corynebacterium jeikeium*and, resistant strains of *Streptococcus pneumoniae*. (An et al., 2011).

Vancomycin is a glycopeptide obtained from *Amycolatopsis orientalis*. It was developed as an active antimicrobial agent for Grampositives, above all, *staphylococci* producers of β-lactamase. It is an alternative drug for penicillin and/or cephalosporin allergic patients (Núñez et al., 2006) with bactericidal activity. Its mechanism of action is to inhibit the synthesis of Gram positive bacterial cell wall at the formation level of polymers of *N*-acetylmuramic acid and *N*-acetylglucosamine or the aminoacid chains interwoven inside peptidoglycan structure (Pootoolal et al., 2002). The use of vancomycin is associated with adverse effects. An adverse reaction to medicines (ARM) is unintentional harmful response to drugs occurring at normal dose when administered in humans for prophylaxis, diagnosis, and treatment of sicknesses, or for the modification of physiologic function. ARMs are public health problem due to the fact that these reactions are often unpredictable and put at risk the life of patients (Limsuwan and Demoly, 2010). Their knowledge could help in predicting the risk

*Corresponding author. E-mail: reparo_gaby@yahoo.com.mx; Tel/Fax: 5255 1084 3883.

of administration and prevention of specific treatments (McAuley, 2012, Edwards and Aronson, 2000). Of these adverse effects to vancomycin, two kinds have been described. The first is anaphylactic immunologic or immediate hypersensitivity mediated by immunoglobulin type E (IgE). The second is IgE independent anaphylactoid reaction, also referred to as non-allergic drug hypersensitivities or pseudoallergic reactions, known as red man syndrome (RMS) (Riedl and Casillas, 2003; Farnam et al., 2012). Nonallergic drug hypersensitivities reaction could occur on first exposition to the drug (Brown, 2009).

Vancomycin could directly activate priming cells or mastocytes, also denominated as granular cells of connective tissue. Mastocytes come from $CD34^+$ precursor cells of the bone marrow. The granules of priming cells or mastocytes contain heparin, histamine, and three classes of neutral protease (tryptase, cymase, and carboxypeptidase). The degranulation could be induced by IgE dependent or independent immune mechanisms (Payne and Kam, 2004). The objective of the present revision work is to bring to knowledge the role of vancomycin in the development of hypersensitivity reactions as well as its underlying mechanisms, and which are the risk factors, its prevention, and treatment so as to improve the administration protocol and avoid iatrogenic events concomitant with its use.

MOLECULAR EVENTS AND CLINICAL MANIFESTATIONS OF ANAPHYLAXIS ASSOCIATED TO VANCOMYCIN

ARM require the creation of awareness on its mechanism of action, especially when anaphylaxis is suspected. Independently of infusion velocity of the medicine, vancomycin induces anaphylaxis through immediate hypersensitivity reaction mediated by IgE. As a consequence of the union of Fc portion of IgE to the receptors of high affinity, FcεRI-α, of priming cell or mastocyte membranes, or the membranes of basophilic cells, a massive release of inflammatory mediators such as histamine, tryptase, prostaglandins, leukotrienes, among others is induced (Bischoff, 2007). The FcεRI-α receptor is expressed in priming cell or mastocyte, and basophilic cells as a heterotetramer composed of one α and β, and two *γ* chains with the last being bonded by disulphuric brigde. The β and *γ* chains are responsible for propagation of signals to the inner part of cells through phosphorylation of the thyroxin-rich activation sites.

The system of signal transductions of FcεRI-Fc receptor induces the activation of kinase of Src family, the formation of macromolecule complexes in the plasmatic membrane, activation of phosphoinositol-calcium exchange route, the phosphorylation of diverse MAP kinases, and controlled transcription of a great number of genes. This signal transduction system regulates degranulation of priming cell or mastocyte and production of cytokines (González et al., 2005).

Many cases of anaphylaxis are due to activation of histamine receptors, and interaction between H1 and H2 receptors, all of which can lead to acute bronchospasm, and wheezing dyspnea as a result of bronchial smooth muscles constriction and mucosal viscosity increase. The combination of the stimulation of H1 and H2 receptors increases vascular permeability, hypotension, tachycardia, and headache. Histamine is not the only agent that produces symptoms of anaphylaxis. The prostaglandins, leukotrienes, and platelet activating factor also play an important role in bronchospasm by increasing vascular permeability and aiding vasodilatation (Bertolissi et al., 2002).

Early diagnosis of anaphylaxis could be achieved by measuring the blood histamine. Unfortunately, the half-life of histamine is short. The tryptase of priming cells or mastocytes could provide an alternative approach to histamine determination (Laroche et al., 1991).

The tryptases are serine tetrameric proteases with a molecular weight of approximately 134 kDa. The enzyme has four subunits, each unit having its active site. The priming cells or mastocytes principally express two types of tryptases: α and β tryptases. β tryptase serves as a marker of the activation of priming cells or mastocytes. The measurement of the concentration of blood tryptase is used to distinguish the reactions dependent on priming cells or mastocytes activation such as anaphylactic and anaphylactoid reactions of other systemic alterations that could simulate similar clinical manifestations (Payne and Kam, 2004).

MOLECULAR EVENTS AND CLINICAL MANIFESTATIONS OF ANAPHYLACTOID REACTIONS ASSOCIATED TO VANCOMYCIN

The red man syndrome is a common adverse event in children receiving vancomycin (Myers et al., 2012). The RMS is characterized by maculopapular rash on the neck, face, and upper part of the trunk, upper and lower extremities and could affect big areas of the body. It could be accompanied by tachycardia or bradycardia which could sometimes lead to cardiac arrest, increase in temperature, scratches, and hypotension with the last being caused by the liberation of histamine which leads to vasodilation and therefore myocardial hypotension and direct inhibition of its function. In majority of the patients, the presence of tachiphylaxis is seen (Kupstaitė et al., 2010).

In lactates, the rash is associated with the reduction of tissue perfusion, cold extremities, increase in the necessity of oxygen and lethargy. This adverse effect could appear during and between 4 - 10 min after the parenteral administration of the first dose of vancomycin. The reaction could disappear after 20 min or persist for

various hours. The severity of the reaction to vancomycin is proportional to the dose administered and the velocity of infusion (Sivagnanam and Deleu, 2003).

Vancomycin induces hypersensitivity reaction (RMS) through IgE independent pathway (Kupstaité et al., 2010). The activation of priming cells or mastocytes, and basophilic leucocytes triggers a cascade of liberation of various pro-inflammatory and vasoactive substances such as histamine, leukotrienes, tumor necrosis factor (TNFα) and platelet activating factor. Histamine is liberated by the granules of priming cells and basophils due to different stimuli such as inflammatory processes, physical agents, drugs like morphine and vancomycin (López, 2009). Great varieties of medicines induce the liberation of histamine from the mastocytes in a direct form and without previous sensitization. All the substances that induce histamine secretion activate the secretory response of the mastocytes or basophils by increasing intracellular ion (Sivagnanam and Deleu, 2003).

Vancomycin is a prototype activator of priming cells or mastocytes, and seems to be partially dependent on calcium for the liberation of histamine and tryptase via mechanisms depending on phospholipase C (PLC) and phospholipase A2 (PLA2). This could be the result of direct action of vancomycin on PLC and PLA2 or by unknown receptor stimulation mechanism (Veien et al., 2000).

The amount of liberated histamine is associated with the velocity of administration and to the concentration of vancomycin in blood (Riedl and Casillas, 2003). Vancomycin prolongs the systemic effect of histamine liberation by inhibiting the action of N-metyltransferase, an enzyme responsible for histamine metabolism (Myers et al., 2012).

Shuto et al. (1999) reported in an *in vivo* and *in vitro* study that muscle relaxing medicines (pancuronium, vecuronium, and succinylcolin) and morphine increase the release of histamine when combined with vancomycin. The intravenous injection of vancomycin in rats (1.25 to 10 mM / 30 min) after morphine administration led to the increase in blood histamine level. These results suggest that vancomycin directly opens calcium Ca^{++} channels and induces the release of histamine. On the other hand, it was believed that morphine activates G proteins. The release of intracellular Ca^{++} induced by these two different mechanisms could contribute synergically to the release of histamine by priming cells or mastocytes. This is observed in the area below histamine curve in correlation to the severity of vancomycin induced erythema. These results show experimental evidences that the combination of muscle relaxing medicines or morphine with vancomycin could increase the risk of anaphylactoid reaction for the increase in the liberation of histamine (Shuto et al., 1999). In 1990, Healy et al. suggested that histamine receptors begin to desensitize due to previous vancomycin exposition and/or other cofactors such as serotonin, bradykinin, cyclic GMP, and PGD2. Moreover, interindividual differences in the sensitivity of histamine receptors could explain why some people release great amount of histamine without presenting a significant reaction with the administration of vancomycin (Healy et al., 1990).

EPIDEMIOLOGY

One of the causes of morbi-mortality in the world is adverse reaction of the medicines provoked by immune and non-immune mechanisms, where iatrogenic represents 5 -15%. In the United States of America, more than 100,000 deaths are attributed to ARM. ARM, including hypersensitivity reactions to medicines, is among the fourth or sixth largest causes of death (Lazarou et al., 1998). Hypersensitivity reactions to medicines (RAM) are seen in 10 - 20% of hospitalized patients (one-third of all the adverse reactions to medicines) and more than 7% of the general population (Limsuwan and Demoly, 2010).

In a retrospective study carried out in a series of 650 children who received vancomycin (12.9 mg/K/dose), 11 cases of RMS were reported accounting to a prevalence of 1.6%. Two of the 11 cases were children less than 8 years old (Levy et al., 1990). On the other hand, in a study of 224 patients (110 males and 114 females) with age range of 19 - 56 years, who were treated with vancomycin for 7.5±9.3 days, the global incidence of adverse reactions was 3 - 6% while the incidence on healthy volunteers who received 1 g of vancomycin in infusion was 80 - 90%. Polk (1991) suggested that the patients who received vancomycin could present less risk of adverse reaction than healthy volunteers possibly for the liberation of histamine that accompany the infection process, malignancy or renal insufficiency.

In a study carried out in healthy volunteers (vancomycin 1g/60min), the incidence of ARM was 80 - 95 and 30% in patients treated with vancomycin 1 g / 120 min. One possible reason for this result is that the infection induced a certain amount of histamine as part of natural immune response that increased histamine concentration which could be associated to a downward regulation of the effect of vancomycin in the mastocytes and basophilic leukocytes. Literature reports indicated that a more severe reaction occurs in patients less than 40 years old, specifically in children (McAuley, 2012). RMS seems to occur with the same frequency not only in men but also in women. The incidence of clinically significant cutaneous reaction related with infusion of vancomycin in patients was less than 5%. Age was a risk factor and could explain the high incidence of 6% in youths with prolonged therapy (Kupstaitė et al., 2010). In another study of 20 children that received 15 mg/kg of vancomycin for 60 min, the patients were monitored along infusion time with the finding that 7 of the children

(35%) developed anaphylactoid reaction induced by glycopeptides, presented hypotension. RMS had an incidence of 3.7 to 47% in patients treated with vancomycin and higher than 90% in healthy patients. In summary, the estimation of RMS incidence widely varies in the studies but all reflect coincidence in the infusion velocity, vancomycin concentration, definition of reaction, observation diligence, study design, inclusion criteria (healthy volunteers or patients), and concomitant medication (Korman et al., 1997).

PREVENTION AND TREATMENT OF RED MAN SYNDROME

In the recent decades, increase in antimicrobial resistance has been observed. It is believed that 25 - 50% of all prescribed antimicrobials are inappropriate with respect to the selection of the medicine, administration doses, and the duration of treatment (Junior et al., 2007). In a random trial of 33 patients treated with vancomycin (1 g/ 60 min) who were previously administered oral diphenhydramine (50 mg), it was found that none of the patients presented RMS. The reaction was seen in 47% of the patients who did not receive pretreatment with diphenhydramine (Wallace et al., 1991).

Fast infusion of vancomycin provokes histamine mediated effects. In a random study of fast infusion of vancomycin (1 g/ 10 min) in 30 pre-operative patients, oral premedication of antihistamines reduced the incidence and severity of RMS. In this study, oral diphenhydramine (≤ 1 mg / kg) administered for 1 h and oral cimetidine (≤ 4 mg / kg) also for 1 h before the infusion were used. The findings were that 50% of the patients treated with placebo developed hypotension while none in the group treated with antihistamines suffered this, although one patient in the latter group complained of mild scratches (Renz et al., 1998). In majority of the patients receiving first-time treatment with vancomycin at an infusion velocity of ≤10 mg/min, premedication with antihistamines for prevention of RMS is not needed. In general, at a dose of ≤ 500 mg/h, or 500 mg to 1 g administrated for more than 2 h, premedication is not necessary. However, an even lower infusion velocity is advised for patients receiving treatment of opioids or other medicines that predispose the activation of priming cells or mastocytes (Kupstaitė et al., 2010). Therefore, RMS could be prevented by decreasing the infusion velocity of vancomycin for at least 1 h (maximum velocity of 1 g for 90 min), monitoring of blood pressure during the infusion, and administration of premedication of antihistamines that block H1 and H2 receptors. The combination of H1 and H2 antagonists is more effective than using only H1 (Sivagnanam and Deleu, 2003). Wazny and Daghigh (2001) suggest that a vancomycin desensitization should be considered for severe RMS and anaphylactic reactions, that is not responding to usual measures, when substitution of another antibiotic is not feasible. A rapid desensitization is preferred as it is effective in the majority of patients, in patients who fail to desensitize rapidly; a slow desensitization protocol may be tried (Wazny and Daghigh, 2001).

VANCOMYCIN AND RISK FACTORS FOR HYPERSENSITIVITY REACTION DEVELOPMENT

The treatment of systemic infections with vancomycin requires the intravenous administration of the medicine, usually by intermittent infusion due to its minimal absorption when orally administered (Revilla, 2009). The interindividual variability of a population in terms of efficacy and safety of therapeutic agents depends on one part on the following factors: age, sex, weight, renal and hepatic functions, co-medication, heterogeneity of the sicknesses, and nutritional state. With respect to the influence of physiologic factors, age is the most important since the expression of maturity state affects pharmacokinetic of medicines suggesting the necessity of establishment of strategies for dose adjustment (Balboa and Rueda, 2004). In newborns, there is a relation between depuration of vancomycin, gestational and postnatal age (Anderson et al., 2007). There are differences in the pharmacokinetic parameters of vancomycin for age effect. In premature (gestational age ≤ 32 weeks), the depuration of vancomycin is less due to a lower glomerular filtration capacity. It is known that filtration and depuration volumes proportionally increase with age due to maturity of the elimination system. The distribution volume is relatively higher in children than in adults for the presence of a higher percentage of water.

Intravenous administration of vancomycin with a unique dose of 500 mg in adults reaches plasma concentrations of 6 to 10 mg/100 ml in 1 or 2 h. The half-life (T1/2) of vancomycin varies depending on the age group. In newborns, it is from 6 - 10 h (10 - 15 mg/kg every 6 – 18 h depending on the age). In infants of 3 - 4 years old, it is 4 h. In children older than 4 years, it is 2.2 – 3 h while in adolescents, it has not been defined. However, there is a hypothesis that puts it at the same with infants (doses for infants, children, and adolescents 10 mg/kg every 6 h) and 5 -8 h in adults (doses of 15 – 20 mg/kg every 6 – 12 h) (Broome and So, 2011). The factors that affect the clinical activity of vancomycin are its tissue distribution, the inoculation site, the bond to protein, and the infusion velocity (Rybak, 2006). The efficacy and toxicity are related to the plasma concentration of the drug. For this, the present clinical guide recommends maintaining the minimal concentration (Cmin), determined at the end of administration interval, at a therapeutic range of 5 and 10 µg/ml, and maximum concentration (Cmax), determined 3 h after intravenous administration, at not more than 40 µg/ml. Apart from RMS, other principal adverse reactions of vancomycin include ototoxicity, nephrotoxicity, and

phlebitis (Rocha et al., 2002).

The kinetic behavior of vancomycin could be modified by different clinical and physiologic factors. The penetration of vancomycin into cerebrospinal fluid is favored by the presence of meningeal inflammation, but the variability of the concentration and minimal inhibitory concentration (MIC) that should be reached needs intraventricular or intrathecal administration in the case of central nervous system infections. Also, access of vancomycin to lung tissue is variable. For this reason, its use by inhalation has been in promotion (Revilla, 2009).

Epidemiological data report the existence of factors increasing the risk of adverse effects such as concomitant sickness like asthma, erythematous lupus, the use of beta blockers, and drug administration. The most important risk factors related to drug hypersensitivity reactions are associated to the chemical properties and to the molecular weight of the drug (Riedl and Casillas, 2003; Schnyder, 2009). The presence of scratch during the administration of vancomycin in infant population could be a sign of alarm indicating the presence of peripheral vasodilatation. This could be opportunely detected in patients that are at a risk of presenting hypotension. The lack of hemodynamic and respiratory changes in patient treated with β-blockers before any surgery probably show that these agents could confer protection against anaphylactoid reactions mediated by histamine liberation (Bertolissi et al., 2002). Women present values of distribution volume greater than men. The difference is even much greater in case of obese women. These data suggest that vancomycin distribution in fat is higher in female. The influence of obesity in the kinetic behavior of this antibiotic has been established showing an increase in the distribution volume and depuration of vancomycin (Penzak et al., 1998).

Conclusion

The red man syndrome is an idiosyncratic phenomenon and does not depend on concentration of vancomycin. To avoid the possible presentation of RMS induced by vancomycin, it is necessary to administrate the drug at an infusion time of at least 1 h. The benefit of antihistaminic prophylaxis to reduce the incidence and severity of RMS, and elaboration of specific guide for its use should be considered.

ABBREVIATIONS

MRSA, Methicillin resistant *Staphylococcus aureus*; **ARM,** adverse reaction to medicines; **IgE,** immunoglobulin type E; **RMS,** red man syndrome; **TNF,** tumor necrosis factor; **PLC,** phospholipase C; **PLA2,** phospholipase A2; **MIC,** minimal inhibitory concentration.

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