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Article

Review on Usage of Vancomycin in Livestock and Humans: Maintaining its Efficacy, Prevention of Resistance and Alternative Therapy

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REVIEW ON USAGE OF VANCOMYCIN IN LIVESTOCK AND HUMANS: MAINTAINING ITS EFFICACY, PREVENTION OF RESISTANCE AND ALTERNATIVE THERAPY

ABSTRACT

Vancomycin is one of the 'last-line' classes of antibiotics used in the treatment of life-threatening infections caused by Gram-positive bacteria. Even though vancomycin was discovered in 1950s it was widely used after 1980s for the treatment of infections caused by methicillin-resistant *Staphylococci* as prevalence of such strains were increased. However, currently it is evident that vancomycin resistant *Staphylococcusaureus*andvancomycin-resistant *Enterococci* have been developed as a result of various reasons including use of avaparcin, which is an analog of vancomycin, as feed additive in livestock. In present day context, more attention should be paid on prevention of emergence of resistance for the antibiotics in order to keep antibiotics effective. In order to prevent emergence of resistance, proper guidance for the responsible use of antimicrobials is indispensable. Therefore, almost all stakeholders who use antibiotics should have in depth understanding on the antibiotic they use. As such, it is imperative to be aware of the important aspects of vancomycin. In the present review, efforts have been made to discussthe pharmacokinetics and pharmacodynamics, indications, emergence of resistance, control of resistance, adverse effects and alternative therapy for vancomycin.

Key words: vancomycin; broad view; veterinary use at a glance; rational use; alternatives

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Research Manuscript section

Introduction

Vancomycin was first discovered from a soil sample in the interior jungle of Borneo in 1950s and its usage was very limited due to the presence of impurities that causes toxicities in the earlier preparations. However, use of vancomycin was reconsidered after emergence of methicillin-resistant *Staphylococci* in the 1970s and its usage was increased from 1980s after purer preparations were made in late 1970s[1].Now vancomycin has become the most common injectable drug of choice to treat methicillin-resistant *Staphylococci* species and drug resistant *Enterococcus* species[2].

Vancomycin exhibit bactericidal activity by inhibiting the cell wall synthesis against aerobic and anaerobic Gram-positive bacteria [3]. Vancomycin and teicoplanin are glycopeptide antibiotics which have bactericidal activity by inhibiting cell wall synthesis against aerobic and anaerobic Gram-positive bacteria. Vancomycin is active against most strains of Clostridia, almost all strains of *Staphylococcus aureus* including those that produce β-lactamases and methicillin resistant strains, coagulase negative Staphylococci, Viridans group Staphylococci and Enterococci. Vancomycin is not effective against Gram-negative bacteria [4]. Vancomycin is one of the antibiotics of last resort, used only after treatment with other antibiotics had failed in the treatment of life-threatening infections by Gram-positive bacteria. Even though vancomycin has great potential in treating infections in animals, the usage of vancomycin in veterinary medicine is limited because it is expensive and the need for continuous intravenous infusion [5]. Available dosage forms of vancomycin are 500 mg, 1g, 5g, 10g vials for injections. Powder of vancomycin is reconstituted in sterile water, which result a dark color solution and it is further diluted in 5% dextrose or saline when it is administered. The reconstituted solution is stable for 14 days either at room temperature or in a refrigerator. 125 mg and 250 mg vancomycin tablets are available for oral administration [6].

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Improper use of antibiotics is largely responsible for the drug-resistance problems, hence, it imperative that a person who intends to use antibiotics eg. vancomycin as a choice of treatment, must know the pro and cons of its affect. In this review efforts, have been made to illustrate the usage of vancomycin in animals and humans, however the review shows areas that need more animal clinical trials as a few information is available for its usage in animals. The limited use of vancomycin in animals is due to various reasons such as it is a last line of antibiotic in human, it is inconvenient to administer in animals, because of emerging vancomycin-resistant *Enterococci* and the threat of spread of vancomycin-resistant genes to other gram-positive organisms. However, vancomycin is a valuable drug of choice for treatment of infections of animals that caused by multi drug resistant *Enterococci* and *Staphylococci* species [7].

Pharmacokinetics and Pharmacodynamics of Vancomycin

Vancomycin is a large glycopeptide compound with a molecular weight of 1448 Da, which inhibits a late stage in bacterial cell wall peptidoglycan synthesis[8,9].Amino acids present in the vancomycin are synthesized and they are joined together and cross linked to assemble vancomycin[10].The three-dimensional structure of vancomycin contains a cleft that fits by hydrogen bonding with the peptides of highly specific configuration of L-alanyl-D-alanyl-D-alanyl which is found only in bacterial cell walls; therefore, vancomycin is selectively toxic by forming stable complexes[11].

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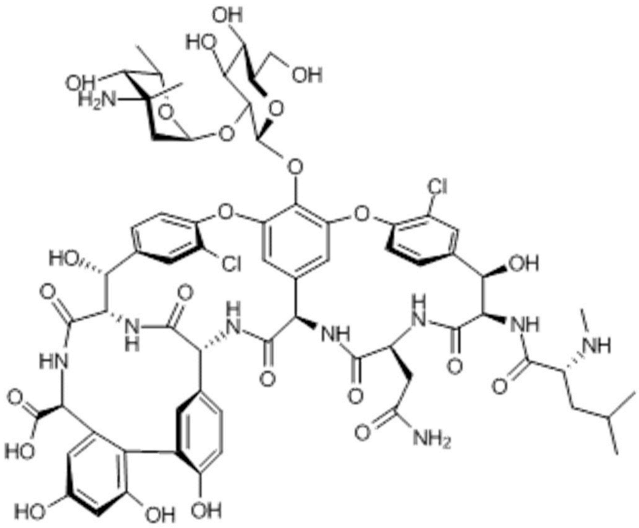

Figure1: Chemical structure of vancomycin [12].

The factors that affect the activity of vancomycin are: its tissue distribution, its protein-binding, inoculum size and resistant organisms. The volume of distribution in humans is 0.4–1 L/kg; in dogs, 0.4- 5.5 L/kg[13].The binding of vancomycin to protein has a range from 10-50%. It has shown in a number of *in vitro* assessments that a 1–8-fold increase in the MIC as a result of the presence of albumin, whereas the presence of serum has had a more variable effect[14,15].It's evident in an in vitro pharmacodynamic model that the time taken to kill is longer when a inoculum size is high (9.5 $\log_{10}$ CFU/g) compared to a moderate inoculum (5.5 $\log_{10}$ CFU/g): 48 versus 72 h for both the methicillin sensitive *Staphylococci* and methicillin-resistant *Staphylococci* organisms isolated from human patients[16,17].

Vancomycin penetrates into most body spaces and the penetrability is dependent on the degree of inflammation present. The concentration of vancomycin in different body spaces is different[18].The inflamed meninges improve penetration of vancomycin into the cerebral spinal fluid, with reported concentrations of 6.4–11.1 mg/L whereas uninflamed meninges, have resulted low concentrations of 0–3.45 mg/L) in human[19].Furthermore, it has been shown in rabbit model that high concentration of

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vancomycin is present in cerebral spinal fluid where there is inflamed meninges [20].Therapeutic concentrations of vancomycin in ascitic, pericardial, pleural and synovial fluids are greater than 2.5 mg/L in human[21].

More than 80% and 50% of a vancomycin dose is excreted unchanged in the urine mostly by way of glomerular filtration within 24 hours after administration in humans and dogs respectively, and the concentration of vancomycin in liver tissue and bile is below detectable levels. vancomycin has a distribution phase of 30 minutes to 1 hour and half-life of vancomycin patients with normal creatinine clearance in humans is about 6 hours; dogs, 2 hours; horses, 3 hours[22,23].

Therefore, it helps to achieve sufficient concentrations of aminoglycosides at the site of the ribosomal target within the enterococci cell for bactericidal activity. Hence, it reduces required high concentrations of aminoglycosides in the extracellular space and thereby bactericidal effect can be achieved by low concentration of aminoglycoside without excessive toxicity[23].

Therapeutic indications of vancomycin

As vancomycin is a last resort of antibiotic in human, its usage in human and animal is limited. That may be the reason for the scarcity of available reference materials on usage of vancomycin in livestock. However, vancomycin would be a compulsory drug of choice in valuable animals such as breeding animals in similar indications of human. Even though the reference material for following indications are mainly deals with human medical conditions, vancomycin can be used in those conditions in animals as vancomycin has been tested in lab animals and it is suggested for clinical trials in animals so as to establish proper guidelines for veterinary clinical practice.

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Significant reduction of number of colony forming units of *Staphylococcus aureus* in mouse blood was observed following vancomycin therapy [11].It has shown that 165 *Enterococcus* strains isolated from dogs were sensitive to vancomycin despite the fact that they show high frequency of resistance to erythromycin, tetracycline, rifampicin, and enrofloxacin[24].

Vancomycin is given for humans by the intravenous route in the prophylaxis when there is a high risk of methicillin-resistant staphylococci and treatment of endocarditis, osteomyelitis, acute bacterial prostatitis and other serious infections caused by Gram positive cocci [25].Human patients with normal renal function should receive an initial dosage of 6.5 to 8 mg of vancomycin per kg intravenously over 1 hour every 6 to 12 hour [26,27].However, the practical dosing intervals can be 8, 12, 24, and 48 hour based on the creatinine clearance of the patient [28].

Currently dosages of vancomycin administration for animals are highly empirical. In general, intravenous administration of vancomycin for animals is at a dose rate of 20 mg/kg over one-hour period at 12 hour intervals diluted in at least 200 mL of 5% dextrose. Vancomycin dosage for horses is 4.3-7.5 mg/kg, 8 hour intervals and for dogs 15 mg/kg 6 hour intervals, intravenously over one-hour period. In dogs, it can be administered a loading dose of 3.5 mg/kg and constant rate infusion of 1.5 mg/kg/hour[2]. Vancomycin can be used to treat for infections caused by erythromycin- and rifampin resistant *Rhodococcus equi* in young horses[29,30].In view of the above it is apparent that the intravenous dose rate of vancomycin for horses falls within the range of human dose rate. However, it is required to execute clinical trials to establish exact dose rates for animals and it is desirable to measure creatinine clearance of animal to decide practical dosing intervals.

Vancomycin is administered locally to treat localized joint or bone infection of horses by regional limb perfusion of 300 mg diluted in a 0.5% solution[2,31]. Vancomycin is given to lobsters suffering from

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gaffkaemia caused due to Gram-positive bacteria, by way of giving injection in to abdominal sinus at a dose rate of 25 mg/kg[32].

Vancomycin is used in human by mouth, a dosage of 125 mg every 6 hours for 7 to 10 days in the treatment of pseudomembranous colitis which is caused by overgrowth of *Clostridium difficile.* The *Clostridium difficile* also causes *Clostridium difficile*-associated diseases in swine, calf and horses[33,34].The empirical dose rate for oral administration in animals is 5-10 mg/kg every 12 hours. Vancomycin can be used orally for *Clostridium perfringens* enteritis and *Clostridium spiroforme* enteritis in rabbits, or *Clostridium difficile* in hamsters[35]and other species, including horses. It has been clinically proven that vancomycin can be used to treat for cholangio-hepatitis caused by a beta-lactam resistant *Enterococcus* in cats at a dose rate of 12- 15 mg/ kg/ hour intravenously[36]Thus, the exact dosage for those indications also should be established with proper dosage intervals.

Vancomycin is added to dialysis fluid in human, in the treatment of peritonitis which caused by vancomycin indicated organisms[37].Animal Clinical trials are suggested to perform in peritoneal dialysis with vancomycin, in cases of acute renal failures and uremia caused by such organisms.

The modified disk diffusion testing has been done to elucidate the synergistic action of vancomycin with ceftriaxone, ceftazidime, cefpodoxime, and amoxicillin-clavulanate against methicillin-resistant staphylococci and it is shown by using a rabbit model that the combination of vancomycin with nafcillin has more efficacy against vancomycin intermediate-susceptible *S. aureus* in aortic valvular vegetation and renal abscesses than by either treatment alone[38].The synergistic action of vancomycin either with gentamicin or streptomycin helps to kill susceptible strains of enterococci[39]. It has been demonstrated in humans that vancomycin is better than trimethoprim-sulfamethoxazole in efficacy and safety in treating staphylococcal infections[40]. As such it is required to conduct animal clinical trials for synergistic action of vancomycin with other drugs.

Emergence of Resistance to Vancomycin

Antibiotic usage either as therapy or prevention of bacterial diseases, or as performance enhancers have resulted in antibiotic resistant micro-organisms in pathogens as well as among bacteria of the endogenous microflora of animals. Antibiotic resistant bacteria present in animals can be transmitted the human via contact or via the food chain. Furthermore, resistance genes of animal bacteria can be transferred to human pathogens in the intestinal flora of humans[32].

It was reported the development of intermediate and high level of resistance to vancomycin for *Staphylococcus aureus* for the first time from surgical wound of an infant of Japan in 1997[41]. According to Clinical Laboratory Standards Institute guidelines, susceptibility break points of vancomycin are ≤ 4 mcg/ mL for *Enterococcus*, ≤1 mcg/ mL for *Streptoccus* and ≤ 4 mcg/ mL for *Staphyloccus*. However, In 2006, the vancomycin MIC breakpoints for *S. aureus* were lowered to 2 µg/mL for "susceptible," 4–8 µg/mL for "intermediate," and 16 µg/mL for "resistant" [42]. Enterococci should be regularly tested *in vitro* for susceptibility to vancomycin for determination of MIC. Enterococci are deemed susceptible to vancomycin if MICs are ≤4µg/mL; they are considered as intermediate level resistance to vancomycin if MICs are 8 to 16 µg/mL and as complete resistance to vancomycin if MICs are >16 µg/ml [23].

Mortality of people has been increased in instances where the MRSA bacteremia caused by strains with a high vancomycin resistance (MIC >1 µg/mL) and when it was treated empirically either with inappropriate antibiotic or vancomycin [43,44,45]. Avoparcin which is a vancomycin analog, is a glycopeptide antibiotic that can suppress the growth of Gram-positive bacteria and it has been used in livestock feed for growth promotion in broiler chickens, growing pigs, calves and beef cattle. Avoparcin has also been used for the purpose of prevention of necrotic enteritis in poultry.In countries where avoparcin was used for above purposes, it was evident that vancomycin-resistant enterococci (VRE) are commonly found in the commensal flora of food animals, on meat from these animals and in the commensal flora of healthy humans in spite of the fact that very low usage of vancomycin in hospitals[32].

The harmless commensals of enterococci have modified over the years to opportunistic pathogens mainly causing nosocomial infections (hospital acquired infections). The development of VRE is one of the products of this phenomenon. The most clinically important bacterial species with resistance gene is *Enterococcus faecium* with vanA type vancomycin resistance which is the most common VRE variant among farm animals, where avoparcin is widely used for growth promotion. When the use of avoparcin was discontinued, the prevalence of VRE among farm animals had been reduced [46,47,48].In vanA type of resistant, D-alanyl-D-alanyl part of bacterial cell wall alters to D- alanyl-D- lactate, thereby it prevents biding of vancomycin to the bacterial cell wall [5].

Table 1. Prevalence of vancomycin resistant enterococci in the fecal flora of healthy animals and humans in the Netherlands [49].

Population	**Number**	**Prevalence of resistant VanAgene (VancomycinVanA)**	**Percentage (%)**
Veal calves	539	92	17

Broilers	51	80	63
Turkeys	50	47	94
Pigs	282	34	12
Dogs and cats	23	17	73
Hospital patients	3	3	100
Urban residents	117	12	10
Outpatients	168	8	4

Control of resistance for vancomycin

The development of preventive strategies to limit existing resistance and to avoid emergence of novel strains of resistant bacteria is the paramount importance in maintaining the efficacy of antibiotics in both human medicine and veterinary medicine. Therefore, understanding the epidemiology of antibacterial resistance will enable us to develop preventive strategies to limit existing resistance and to avoid the emergence of new strains of resistant bacteria. [50,51].

In order to control emergence of resistance, hygienic measures to prevent cross contamination and a decrease in the usage of antibiotics are very vital aspects. The reduction of the need for antibiotics is the best possible way of controlling resistance in large groups of animals. This can be accomplished by proper vaccination against infectious diseases, adoption of good hygienic practice in animal husbandry, stopping the use of antibiotics as feed additives for growth promotion in animals bred as a food source, appropriate use of antibiotics for food animals and development of guidelines, codes of practice and policies on appropriate use of antibiotics. Farm workers and owners of pets being treated with antibiotics need to pay due attention to hygiene during and after handling treated animals[32].

In an infection caused by MRSA strains with elevated vancomycin MIC (2 µg/mL) needs elevated vancomycin dosing to achieve a serum concentration of vancomycin greater than 15 µg/mL. In order to get such concentrations, it is required to increase the recommended dosage. That may cause toxicities. Hence, a combination or alternative therapy should be considered for such infections[52,53].Efficacy of the vancomycin can be achieved by using of individualized doses of vancomycin based on MIC values for the bacterial strain and physiological condition of the animal[54].Vancomycin usage in animal should be restricted for infections which response only to vancomycin and there are no other reasonable alternatives and when it is used in animals, it should be given at proper dosage, proper dosage interval and proper duration of treatment[29].

Adverse Effect of vancomycin

Although there is a little information on toxicity in animals, there is a high possibility in animals for following adverse effects which are evident in human clinical trials [5]. It is reported that vancomycin administration may lead to fatal enterotoxaemia in guinea pigs [37].

Prolonged intravenous use of vancomycin may cause neutropenia, thrombophlebitis, rash, fever, anemia, thrombocytopenia, and ototoxic reactions in humans as well as animals. As vancomycin is highly tissue irritant drug it should be administer intravenous route in diluted form. It may cause local phlebitis at the site of injection in animals [6,8]. Vancomycin should be infused for ≥1 hour to reduce the risk of the histamine release–associated "red man" syndrome in humans. It is advised not to administer rapidly intravenous, so as to avoid acute adverse reaction in animals [2]. The major drawback of vancomycin usage

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is auditory damage in human; however, tinnitus and deafness might improve once the treatment is ceased. In addition to that it has been observed nausea, chills, phlebitis, severe hypotension, wheezing, dyspnoea, urticaria, pruritus with the treatment of vancomycin in human [55,56,57,58]. In some instances, with prolonged therapy neutropenia was detected [59].

There is a potential for nephrotoxicity and ototoxicity with vancomycin in animals [60]. Toxicities are minimal in vancomycin monotherapy at conventional dosages of 1 g (15 mg/kg) every 12 hours in human [61].However, increased incidence of nephrotoxicity has been established with doses of 4 g/day or higher. As a result of elevated dosage, serum concentrations may increase and it may lead to toxicity[62,63,64,65].Vancomycin increases risk of nephrotoxicity in human with drugs such as aminoglycosides, amphotericin, capreomycin,cyclosporine,cisplatin,colistimethate, polymyxins and tacrolimus[37].There are veterinary indications for above drugs[66,67].Therefore, it is desirable to investigate the adverse effects when above drugs are administered concurrently with vancomycin in animals.

Alternative Therapy for Vancomycin

Alternative therapies should be considered for human with the *S. aureus* infections that show a vancomycin MIC of 2 mg/L or greater than that [44]. Lysostaphin, an endopeptidase is more effective than vancomycin in treating meticillin-resistant *Staphylococcus aureus* in a neonatal pup model [15,24].

Oral bacitracin can be considered as an alternative to vancomycin in the treatment of antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* cytotoxin in animals. Bacitracin is used for the bacitracin sensitive infections in pigs, chicken and turkeys [60].

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Linezolid which is an oxazolidinone, active against Gram-positive bacteria is one of the options for vancomycin in the treatment of infections that are caused by antibacterials including meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci infections in human. It has been shown in murine model that linezolid can be used to control *Mycobacterium tuberculosis* infection. Linezolid are also used in dogs. Moreover, linezolid is used in animal for the treatment of nocardiosis. Therefore, it is required to establish efficacy and dose rates for linezolid in animals [68,69].Prolonged usage and the dose less than that recommended may lead to development of resistance to linezolid. As linezolid is not active against Gram-negative organisms it must be coupled with other antibacterial, if the infection involves both Gram-positive and Gram-negative organisms and this combination should be used for infections only when other treatments are not available[70].It has demonstrated in rat model that linezolid with rifampin or vancomycin with rifampin is effective in an animal model of MRSA foreign body osteomyelitis[71].Teicoplanin having similar activity on MRSA with minimal renal toxicity [72].

Other therapeutic options for vancomycin are trimethoprim-sulfamethoxazole, doxycycline or minocycline either with or without rifampin. Although vancomycin is superior to trimethoprim-sulfamethoxazole in efficacy and safety, trimethoprim-sulfamethoxazole can be given in selected cases of MRSA infection wherein vancomycin treatment failures [40].All of the above drugs are used in animals[60].Rifampin can be used to treat pneumonic condition in foals caused by *Rhodcoccus equi* at a dose rate of 5 to 10mg/ kg orally at 12 hour intervals. Rifampin has been suggested to use for the treatment of atypical bacterial infection in cats [5,60].Further the novel anti-MRSA cephalosporin ceftobiprole is at the pipeline. Veterinary use need to elucidate.

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It is shown in chicks that dietary cell-wall preparation of *Enterococcus faecalis* strain EC-12 can be used to stimulate the gut immune system and to reinforce the immune reaction against the vancomycin resistant enterococci [73].

Conclusions

As vancomycin is a last resort of antibiotic where other antibiotics cannot be used, it is essential to maintain efficacy of vancomycin for treating humans, pet animals and livestock species. In order to achieve above mentioned objective, vancomycin should be used only instances where it is necessary to be used with proper dosing, dosing interval and appropriate duration of treatment based on MIC values of the disease-causing agent, physiological condition of the animal, and combination of antibiotics where appropriate. There are scant research exists on usage of vancomycin in animals. According to the facts discussed in this review, it is required to establish novel parameters in clinical usage of vancomycin in treating animals, by animal clinical trials in order to minimize the emerging antibiotic resistance of micro-organisms against vancomycin in animals and transferring those organisms to humans. Some countries prohibited using vancomycin analogues in animal food additives which seems a late decision because vancomycin resistant genes already evolved before they ban those feed additives. Therefore, vigilance on antibiotic resistance is useful to prevent such incidents in future.

Back Matter

Author contribution- All four authors contributed equally for this work

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