VANCOMYCIN HIKMA®

Sterile Vancomycin Hydrochloride

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration; it is given intravenously for therapy of systemic infections. Intramuscular injection is painful. In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean serum concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL two hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL eleven hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 18 mcg/mL two hours after infusion, and mean plasma concentrations of about 10 mcg/mL six hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In the first 24 hours, about 75% of an administered dose of vancomycin is recovered in urine by glomerular filtration. Mean plasma clearance is about 0.058 L/kg/hr, and mean renal clearance is about 0.048 L/kg/hr. Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days. The distribution coefficient is from 0.3 to 0.43 L/kg. There is no apparent metabolism of the drug. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in six hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. Although vancomycin is not effectively removed by either hemodialysis or peritoneal dialysis, there have been reports of vancomycin clearance with hemoperfusion and hemofiltration. Total systemic and renal clearance of vancomycin may be reduced in the elderly. Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After I.V. administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

MICROBIOLOGY

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is active against *staphylococci, including Staphylococcus aureus and Staphylococcus epidermidis (including heteroglanous methicillin-resistant strains); streptococci, including Streptococcus pyogenes, Streptococcus pneumoniae (including penicillin-resistant strains), Streptococcus agalactiae, the viridans group, Streptococcus bovis, and enterococci (e.g., Enterococcus faecalis (formerly Streptococcus faecalis); Clostridium species (e.g., Clostridium difficile-associated pseudomembranous enterocolitis); and diphtheroids. Other organisms that are susceptible to vancomycin in vitro include Listeria monocytogenes, Lactobacillus species, Actinomyces species, Clostridium species, and Bacillus species. In vitro* resistance to vancomycin has been reported among some *enterococcal and staphylococcal isolates.* Vancomycin is not active in vitro against *gram-negative bacilli, mycobacteria, or fungi.*

Synergy: The combination of vancomycin and an aminoglycoside acts synergistically in vitro against many strains of *S. aureus, nonenterococcal group D streptococci, enterococci, and Streptococcus species (viridans group).*

Disk Susceptibility Tests - The standardized disk method described by the National Committee for Clinical Laboratory Standards has been recommended to test susceptibility to vancomycin. Results of standard susceptibility tests with a 30 mcg vancomycin hydrochloride disk should be interpreted according to the following criteria: Susceptible organisms produce zones greater than or equal to 12 mm, indicating that the test organism is likely to respond to therapy. Organisms that produce zones of 10 or 11 mm are considered to be of intermediate susceptibility. Organisms in this category are likely to respond if the infection is confined to tissues or fluids in which high antibiotic concentrations are attained. Resistant organisms produce zones of 9 mm or less, indicating that other therapy should be selected. Using a standardized dilution method, a bacterial isolate may be considered susceptible if the MIC value for vancomycin is 4 mcg/mL or less. Organisms having an MIC value of 8 to 16 mcg/mL are considered to be of intermediate susceptibility. Standardized procedures require the use of laboratory control organisms. The 30 mcg vancomycin disk should give zones diameters between 15 and 19 mm for S. aureus ATCC 25923. As with the standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard vancomycin powder should give MIC values in the range of 0.5 mcg/mL to 2.0 mcg/mL for S. aureus ATCC 29213. For E. faecalis ATCC 29212, the MIC range should be 1.0 to 4.0 mcg/mL.

INDICATIONS

Vancomycin hydrochloride is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (ß-lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-resistant organisms that are resistant to other antimicrobial drugs. Vancomycin is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly. Vancomycin is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in bone infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, and skin and skin-structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures. Vancomycin has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by S. viridans or S. bovis. For endocarditis caused by enterococci (e.g., E. faecalis), vancomycin has been reported to be effective only in combination with an aminoglycoside. Vancomycin has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin has been used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by S. epidermidis or diphtheroids. Specimens for bacteriological studies should be obtained in order to identify causative organisms and to determine their susceptibilities to vancomycin. The parenteral form of vancomycin may be administered orally for treatment of antibiticsassociated pseudomembranous colitis produced by C. difficile and for staphylococcal enterocolitis. Parenteral administration of vancomycin alone is of unproven benefit for these indications. Vancomycin is not effective by the oral route for other types of infection. Although no controlled clinical efficacy studies have been conducted, intravenous vancomycin has been suggested by the American Heart Association and the American Dental Association as prophylaxis against bacterial endocarditis in penicillin-allergic patients who have congenital heart disease or rheumatic or other acquired valvular heart disease who undergo dental procedures or surgical procedures of the upper respiratory tract. NOTE: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association. To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Sterile vancomycin hydrochloride is contraindicated in patients with known hypersensitivity to this antibiotic.

DOSAGE AND ADMINISTRATION

Infusion-related events are related to both concentration and rate of administration of vancomycin. Concentrations of no more than 5 mg/mL and rates of no more than 10 mg/min are recommended in adults. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusion-related events may occur, however, at any rate or concentration.

Patients with Normal Renal Function

Adults: The usual daily intravenous dose is 2 g divided either as 500 mg every six hours or 1 g every 12 hours. Each dose should be administered over a period of not less than 60 minutes, or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual daily dose.

Pediatric Patients: The usual intravenous dosage of vancomycin is 10 mg/kg per dose given every six hours. Each dose should be administered over a period of at least 60 minutes. Infants and Neonates: In neonates and young infants, the total daily intravenous dosage of 15 mg/kg is recommended. In neonates and infants, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every eight hours thereafter up to the age of one month. Each dose should be administered over 60 minutes. Close monitoring of serum concentrations of vancomycin may be desirable in these patients.

Patients with Impaired Renal Function and Elderly Patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assays, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography. If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated from the following table. The dosage of vancomycin per day in mg is about 15 times the glomerular filtration rate in mL/min.

DOSAGE TABLE FOR VANCOMYCIN

IN PATIENTS WITH IMPAIRED RENAL FUNCTION

	Creatinine Clearance / Vancomycin Dose									
mL/min	100	90	80	70	60	50	40	30	20	10
mg/24 h	1545	1390	1235	1080	925	770	620	465	310	155

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency. The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be given in order to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 h. In patientswith marked renal impairment, it may be more convenient to give maintenance doses of 250 to1000 mg every several days rather than administering the drug on a daily basis. In anuria, adose of 1000 mg every 7 to 10 days has been recommended. When only serum creatinine concentration is known, the following formula (based on sex, weight, and age of the patient) may be used to calculate creatinine clearance. Calculated creatinine clearances (mL/min) are only estimates. The creatinine clearances should be measured promptly. **Men:** $\frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine concentration (mg/dL)}}$ **Women:** 0.85 x above value

The serum creatinine must represent a steady state of renal function or the estimated value for creatinine clearance will not be valid. Such a calculated clearance is an overestimate of actual clearance in patients with conditions: (1) characterized by decreasing renal function, such as shock, severe heart failure, or oliguria; (2) in which a normal relationship between muscle mass and total body weight is not present, such as in obese patients or those with liver disease, edema, or ascites; and (3) accompanied by debilitation, malnutrition, or inactivity. The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) route have not been assessed. Intermittent infusion is the recommended method of administration.

PREPARATION AND STABILITY

At the time of use, reconstitute by adding either 10 mL of Sterile Water for Injection to the 500-mg vial or 20 mL of Sterile Water for Injection to the 1 g vial of dry, sterile vancomycin powder.

FURTHER DILUTION IS REQUIRED.

After reconstitution with Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, the vials may be stored in a refrigerator for 14 days without significant loss of potency. Reconstituted solutions containing 500 mg of vancomycin must be diluted with at least 100 mL of diluent. Reconstituted solutions containing 1 g must be diluted with at least 200 mL of diluent. The desired dose, diluted in this manner, should be administered by intermittent intravenous infusion over a period of at least 60 minutes. Solutions of vancomycin hydrochloride reconstituted with Sterile Water for Injection contain no bacteriostat and are intended for use only as a single-dose injection. When smaller doses are required, the unused portion should be discarded. When reconstituted with sterile water for injection, further dilution is required before use. Vancomycin hydrochloride is prepared as a solution and lyophilized in its final container.

Compatibility with Other Drugs and Intravenous Fluids

Solutions that are diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection may be stored in a refrigerator for 14 days without significant loss of potency. Solutions that are diluted with the following infusion fluids may be stored in a refrigerator for 96 hours: 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Lactated Ringer's and 5% Dextrose Injection, Normosol®-M and 5% Dextrose, ISOLYTE® E. Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds. Mixtures of solutions of vancomycin and beta-lactam antibiotics have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to administer by separate intravenous lines between the administrations of these antibiotics. It is also recommended to dilute solutions of vancomycin to 5 mg/mL or less. Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles. The precipitates dissolved gradually, with complete clearing of the vitreous cavity over two months and with improvement of visual acuity. Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permits.

For Oral Administration: Oral vancomycin is used in treating antibiotic-associated pseudomembranous colitis caused by C. difficile and for staphylococcal enterocolitis. Vancomycin is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g given in 3 or 4 divided doses for 7 to 10 days. The total daily dosage in pediatric patients is 40 mg/kg of body weight in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g. The appropriate dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.

WARNINGS

Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension and, rarely, cardiac arrest. Vancomycin should be administered in a diluted solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions. Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations. Dosage of vancomycin must be adjusted for patients with renal dysfunction. Pseudomembranous colitis has been reported with nearly all antibacterial agents including vancomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of antibiotic-associated colitis. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluid and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile* colitis.

PRECAUTIONS

General: Clinically significant serum concentrations have been reported in some patients who have taken multiple oral tablets of vancomycin for active C. difficile-induced pseudomembranous colitis. Prolonged use of vancomycin may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.In order to minimize the risk of nephrotoxicity when treating patients with underlying *renal dysfunction* or patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function and appropriate care should be given to the dosage regimen to prevent excessive dosing schedule. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity. Reversible neutropenia has been reported in patients receiving vancomycin. Patients who will undergo prolonged therapy with vancomycin or who have been receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count. Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur with intramuscular injection of vancomycin or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly (2.5 to 5 g per hour) in a dilute solution (0.5 g in 100 mL) and by rotating the sites of infusion. There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythemia, urticaria, and pruritus) increases with the concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of vancomycin as a 60-minute infusion prior to anesthetic induction. The safety and efficacy of vancomycin administered via the intrapleural (intralumbar or intraventricular) route have not been assessed. Reports have revealed that administration of sterile vancomycin HCl by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. To date, this syndrome has largely been reported alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be short-lived after discontinuation of intraperitoneal vancomycin. Prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions. Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, or cisplatin, should be avoided unless clearly indicated.

Pregnancy: Teratogenic Effects, Category C. Animal reproduction studies have not been conducted with Vancomycin HCl. It is not known whether Vancomycin HCl can affect reproduction capacity. In a controlled clinical study, the potential adverse effects of Vancomycin HCl on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin HCl was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant whose mother received vancomycin in the third trimester experienced conductive hearing loss that was not related to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Vancomycin is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman. Consideration should be given to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients.

Geriatrics: The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients.

Information for Patients: Patients should be counseled that antibacterial drugs including vancomycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When vancomycin is prescribed to treat a bacterial infection, the patient should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by vancomycin or other antibacterial drugs in the future.

SIDE EFFECTS

Infusion-Related Events: During or soon after rapid infusion of vancomycin, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body ("Red Man Syndrome") or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. Such events are infrequent if vancomycin is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion related events did not occur when vancomycin was administered at a rate of 10 mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of vancomycin, has been reported.

Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin was discontinued, azotemia resolved in most patients.

Ototoxicity: A few dozen cases of hearing loss associated with vancomycin have been reported. Most of these were in patients with a preexisting hearing loss, or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic: Reversible neutropenia, usually starting one week or more after onset of therapy with vancomycin or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported. Although a causal relationship has not been established, reversible agranulocytosis (granulocytes < 500/mm³) has been reported rarely.

Phlebitis: Inflammation at the injection site has been reported.

Gastrointestinal: Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Miscellaneous: Infrequently, patients have been reported to have had anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), linear IgA bullous dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with the administration of vancomycin. Chemical peritonitis has been reported following intraperitoneal administration of vancomycin.

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemodialysis or hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.The median lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice. To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

STORAGE

Store at controlled room temperature 15° to 30°C (59° to 86°F).

PRESENTATIONS

Vials

VANCOMYCIN HIKMA 500 mg: Sterile Vancomycin Hydrochloride (equivalent to 500 mg vancomycin)

VANCOMYCIN HIKMA 1000 mg: Sterile Vancomycin Hydrochloride (equivalent to 1000 mg vancomycin)

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of the reach of children

Manufactured by Hikma Italy, SpA, Illay
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