

Vancomycin Hydrochloride for Injection, USP **Antibiotic**

ACTIONS

The inhibition of cell wall synthesis has been shown by *in vitro* studies to be responsible for the bactericidal action of vancomycin against many gram-positive bacteria. There is also evidence that RNA synthesis is selectively inhibited and the permeability of the cell membrane is altered by vancomycin.

INDICATIONS AND CLINICAL USES

Vancomycin Hydrochloride for Injection, USP is indicated in the therapy of severe or life-threatening staphylococcal infections in patients who cannot receive or have failed to respond to the penicillins or cephalosporins or who have infections with staphylococci resistant to other antibiotics, including methicillin.

In the treatment of staphylococcal endocarditis, vancomycin has been used successfully alone.

In other infections due to staphylococci, including osteomyelitis, pneumonia, septicemia and soft-tissue infections, vancomycin's effectiveness has been documented. Antibiotics are used as adjuncts to appropriate surgical measures when staphylococcal infections are localized and purulent.

Although no controlled clinical efficacy trials have been conducted, intravenous vancomycin has been suggested by the American Heart Association and the American Dental Association as prophylaxis against bacterial endocarditis in patients allergic to penicillin who have congenital and/or rheumatic or other acquired valvular heart disease when they 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.)

For the treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*, vancomycin should be used orally. Parenteral administration of vancomycin is not effective for these indications, therefore vancomycin must be given **orally**. For the treatment of other types of infection, vancomycin is not effective by the oral route.

Specimens for bacteriological cultures should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to vancomycin.

CONTRAINDICATIONS

Vancomycin Hydrochloride for Injection, USP is contraindicated in patients with known hypersensitivity to the antibiotic.

WARNINGS

Exaggerated hypotension, including shock, and rarely cardiac arrest may result from rapid bolus administration (e.g., over several minutes) of vancomycin hydrochloride.

Toxic serum levels can occur when given intravenously. Vancomycin is excreted fairly rapidly by the kidney and, with decreased renal clearance, blood levels increase markedly. The risk of toxicity appears appreciably increased by high blood concentrations or prolonged treatment during parenteral therapy. Orally, vancomycin is poorly absorbed. Therefore, toxic serum levels are not attained from oral dosage.

When serum levels exceed 80 µg/mL, ototoxicity has occurred. Tinnitus may precede deafness. The elderly are more likely to experience auditory damage. Deafness may be progressive despite cessation of treatment, as experience with other antibiotics suggests.

Careful monitoring is required with concurrent and sequential use of other neurotoxic and/or nephrotoxic agents, particularly aminoglycoside antibiotics, cephaloridine, polymyxin B, colistin, viomycin, paromomycin, cisplatin and neuromuscular blocking agents.

If parenteral and oral vancomycin are administered concomitantly, an additive effect may occur, which should be considered when calculating the total dose given. Levels of vancomycin in serum should be monitored in these circumstances.

PRECAUTIONS

To avoid rapid infusion-related reactions, Vancomycin Hydrochloride for Injection, USP should be administered in a dilute solution over a period of not less than 60 minutes. A prompt cessation of these reactions usually results when the infusion is stopped (see **DOSE AND ADMINISTRATION** and **ADVERSE REACTIONS**).

Vancomycin hydrochloride should be used with care in patients with renal insufficiency because of its ototoxicity and nephrotoxicity. The dose and/or dose intervals should be adjusted carefully and blood levels monitored if it is necessary to use vancomycin parenterally in patients with renal impairment.

In patients with previous hearing loss, vancomycin should be avoided (if possible). If used in such patients, the dose of vancomycin should be monitored by periodic determination of drug levels in blood. Serial tests of auditory function and of vancomycin blood levels should be performed in patients with renal insufficiency and in individuals over the age of 60. Periodic hematologic studies, urinalyses, and liver and renal function tests should be taken in all patients receiving vancomycin.

The overgrowth of non-susceptible organisms may result with the use of vancomycin. Appropriate measures should be taken if new infections due to bacteria or fungi appear during therapy with this product. These measures should include the withdrawal of vancomycin.

In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received intravenous vancomycin.

Vancomycin should never be given intramuscularly. Vancomycin is irritating to tissue and causes drug fever, pain and possibly necrosis if injected intramuscularly. Therefore, it must be administered intravenously. In many patients receiving vancomycin, pain and thrombophlebitis occur and are occasionally severe. By administering the drug in a volume of at least 200 mL of glucose or saline solution and by rotating the sites of injection, the frequency and severity of thrombophlebitis can be minimized.

The frequency of infusion-related events (including hypotension, flushing, erythema, urticaria and pruritus) has been reported to increase with concomitant administration of anesthetic agents. The administration of vancomycin hydrochloride as a 60-minute infusion prior to anesthetic induction may minimize infusion-related events.

The safety and efficacy of administering vancomycin by the intrathecal (intralumbar or intraventricular) route have not been assessed.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral vancomycin and may thus be at risk of developing adverse reactions associated with parenteral administration of vancomycin. This risk is greater in the presence of renal impairment. Total systemic and renal clearance of vancomycin are reduced in the elderly.

When patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.

Use In Pregnancy

Vancomycin should be given during pregnancy only if clearly needed. Vancomycin levels of 13.2, and 16.7 µg/mL were measured in cord blood of 2/10 pregnant women treated with vancomycin in a controlled clinical study of serious staphylococcal infection complicating intravenous drug abuse. Because the number of patients treated in this study was small and vancomycin administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm.

Nursing Mothers

Vancomycin is excreted in human milk. Caution should be exercised if vancomycin is administered to a nursing mother. The potential for adverse effects warrants that a decision be made whether to discontinue nursing of the infant or administration of vancomycin, taking into account the importance of the drug to the nursing mother.

Pediatrics

In premature neonates and in young infants, it may be advisable to confirm desired serum levels of vancomycin.

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in children.

Geriatrics

Vancomycin dosage levels should be adjusted in elderly patients. The natural decrease in glomerular filtration rate with increasing age may lead to elevated concentrations of vancomycin in serum if dosages are not adjusted.

Burn Patients

Burn patients reportedly have higher total body clearance rates for vancomycin and may thus require more frequent and higher doses. Dosage individualisation and close monitoring of burn patients being treated with vancomycin may be warranted.

ADVERSE REACTIONS

Infusion-related Events

Associated with the administration of vancomycin hydrochloride are nausea, chills, fever, wheezing, dyspnea, pruritis, urticaria and macular rashes. Eosinophilia and anaphylactoid reactions may also be produced. A throbbing type of pain in the muscles of the back and neck has been described and can usually be minimized or avoided by

slower administration (see **DOSAGE AND ADMINISTRATION**). There have been reports of hypotension which is more apt to occur with rapid administration. During rapid administration, flushing of the skin over the neck and shoulder with transitory fine rash including urticaria ("red neck") has also been observed. These reactions may persist for several hours but usually resolve within 20 - 30 minutes.

Nephrotoxicity

Renal failure has been reported rarely in patients treated with vancomycin, principally manifested by increased serum creatinine or BUN, particularly in patients given large doses. Most of these have occurred in patients who had pre-existing kidney dysfunction or who were given aminoglycosides concomitantly. Azotemia resolved in most patients upon discontinuance of vancomycin. Rare cases of interstitial nephritis have been reported in patients treated with vancomycin.

Ototoxicity

Hearing loss associated with vancomycin has been reported by approximately two dozen patients. In most cases, patients also had kidney dysfunction, pre-existing hearing loss or concomitant treatment with an ototoxic drug. Rarely have there been reports of vertigo, dizziness and tinnitus.

Hematopoietic

The development of reversible neutropenia, usually starting one week or more after onset of therapy with vancomycin or after a total dose of more than 25 g has been reported, including some 24 "spontaneous cases" from published reports and other sources. Upon discontinuance of vancomycin, neutropenia appears to be promptly reversible. Thrombocytopenia has been reported rarely. Reversible agranulocytosis (granulocyte count less than 5000/mm³) has been reported rarely.

Phlebitis

Inflammation at the injection site has been reported.

Miscellaneous

Drug fever, exfoliative dermatitis, Stevens-Johnson syndrome, and rare cases of vasculitis have been associated with the administration of vancomycin.

TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Hemofiltration and hemoperfusion with polysulfone resins reportedly result in increased clearance of vancomycin. As no specific antidote is known, general supportive treatment is indicated. Significant amounts of vancomycin are not removed by dialysis.

DOSAGE AND ADMINISTRATION

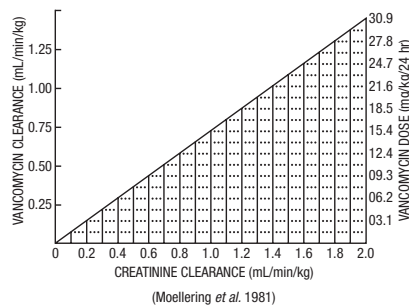
Each dose should be administered at a rate of no more than 10 mg/min or over a period of at least 60 minutes.

Intravenous Dosage

Adults: The usual intravenous dose is 500 mg every 6 hours or 1 g every 12 hours. Other patient factors such as age or obesity may call for modification of the usual intravenous daily dose.

Adults with Impaired Renal Function: To avoid toxic serum levels, dosage adjustment is required in patients with impaired renal function. Since accumulation in such patients has been reported to occur over several weeks of treatment, serum levels should be checked regularly.

The dosage calculation may be made by using the following nomogram if the creatinine clearance value is known for most patients with renal impairment or the elderly:



For functionally anephric patients on dialysis, the nomogram is not valid. In order to achieve therapeutic serum levels promptly in such patients, a loading dose of 15 mg/kg of body weight should be given. The dose required to maintain stable serum levels is 1.9 mg/kg/24 h.

When only serum creatinine is available, the conversion of this value into estimated creatinine clearance may be accomplished by using the following formula based on sex, weight and age of the patient.

A steady state of renal function is represented by the serum creatinine.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

Neonates, Infants and Children: The dosage schedule which follows has been used. Infusions can be divided and incorporated in the child's 24-hour fluid requirement and should be infused over 60 minutes.

Infants and Neonates: It is suggested that an initial dose of 15 mg/kg be administered followed by 10 mg/kg every twelve 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 given over 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Children: The usual i.v. dosage of vancomycin is 10 mg/kg given every six hours.

The majority of patients with infections caused by organisms susceptible to the antibiotic demonstrate a therapeutic response by 48 to 72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, therapy for three weeks or longer is recommended.

Oral Dose

Vancomycin, when administered orally, is to be used only in the treatment of staphylococcal enterocolitis, and/or pseudomembranous colitis associated with toxigenic *Clostridium difficile*.

Adults: The usual daily dose for antibiotic-associated colitis and/or staphylococcal enterocolitis is 125 - 500 mg orally every 6 - 8 hours for 7 - 10 days.

Children: The usual daily dosage is approximately 40 mg/kg in 3 or 4 divided doses for 7 - 10 days. The total daily dose should not exceed 2 g.

Administration

Intermittent Intravenous Infusion: It is necessary to **further dilute** the reconstituted solution with 100 - 200 mL Normal Saline or D5W (dextrose in sterile water for injection). The infusion should be over a period of at least 60 minutes. See the **RECONSTITUTION** section for instruction.

Continuous Intravenous Infusion: Only when intermittent infusion is not practical should continuous intravenous infusion be used. A concentration no greater than 10 mg/mL is recommended. An infusion of 10 mg/min or less is associated with fewer infusion-related adverse events.

Oral Administration: By diluting the contents of the i.v. vial (500 mg) in 30 mL of water, the patient is permitted to drink the antibiotic or the solution may be administered via nasogastric tube.

DESCRIPTION

Vancomycin hydrochloride is an off-white to light-tan lyophilized plug. It forms a clear, colourless solution with a pH range of 2.5 to 4.5 when reconstituted in water.

COMPOSITION

Each vial contains vancomycin hydrochloride equivalent to 500 mg, 1 g, 5 g and 10 g vancomycin base.

STABILITY AND STORAGE RECOMMENDATIONS

Store the unreconstituted product between 15 and 30°C.

RECONSTITUTION

500 mg vial: The addition of 10 mL of Sterile Water for Injection provides a reconstituted solution containing approximate average vancomycin concentration of 50 mg/mL.

1 g vial: The addition of 20 mL of Sterile Water for Injection provides a reconstituted solution containing approximate average vancomycin concentration of 50 mg/mL.

5 g vial: The addition of 100 mL of Sterile Water for Injection provides a reconstituted solution containing approximate average vancomycin concentration of 50 mg/mL.

Note: Further dilution is required.

10 g vial: The addition of 95 mL of Sterile Water for Injection provides a reconstituted solution containing approximate average vancomycin concentration of 100 mg/mL.

Note: Further dilution is required.

For Intermittent Intravenous Infusion

500 mg vial: Dilution of reconstituted solutions is required using at least 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose in Sterile Water for Injection.

1 g vial: Dilution of reconstituted solutions is required using at least 200 mL of 0.9% Sodium Chloride Injection or 5% Dextrose in Sterile Water for Injection.

5 g vial: Further dilution of the reconstituted solution is required. The 5 g vial is a Pharmacy Bulk Package intended for pharmacy use only.

10 g vial: Further dilution of the reconstituted solution is required. The 10 g vial is a Pharmacy Bulk Package intended for pharmacy use only.

For Continuous Intravenous Infusion

The vial contents are first reconstituted by adding Sterile Water for Injection as follows:

500 mg vial: add 10 mL of Sterile Water for Injection

1 g vial: add 20 mL of Sterile Water for Injection

The reconstituted solution is then added to one of the following i.v. solutions:

5% Dextrose Injection

5% Dextrose and 0.9% Sodium Chloride Injection

0.9% Sodium Chloride Injection

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Single-dose vials. Discard unused portion.

Pharmacy Bulk Package

The availability of the Pharmacy Bulk Package is restricted to hospitals with a recognized intravenous admixture program.

Directions for Dispensing From Maxivials (Pharmacy Bulk Package): Vancomycin Hydrochloride for Injection, USP is available in a **single use** vial for pharmacy use only, referred to as a Maxivial[®]. Like the single-dose vial, **Maxivial[®] is not for direct infusion**. Maxivial[®] comes with a hanging vial label and should be suspended as a unit in a laminar flow hood. Entry into the vial must be made with a sterile dispensing device and contents dispensed in aliquots using aseptic technique (see **DOSAGE AND ADMINISTRATION**). Use of syringe/needle is not recommended as it may cause leakage. **Any unused portion of the reconstituted stock solution should be discarded within 8 hours after initial entry.**

STABILITY OF SOLUTIONS

Storage

If stored at room temperature, reconstituted solutions and further diluted infusion mixtures should be used within 24 hours. However, if stored under refrigeration (4°C), they should be used within 96 hours.

Incompatibility

The following are some of the specific substances found to be incompatible: aminophylline, amobarbital sodium, chloramphenicol sodium succinate, chlorothiazide sodium, dexamethasone sodium phosphate, methicillin sodium, vitamin B complex with C, heparin sodium, penicillin G potassium, phenobarbital sodium, phenytoin sodium, secobarbital sodium, sodium bicarbonate and warfarin sodium.

AVAILABILITY OF DOSAGE FORMS

Vancomycin Hydrochloride for Injection, USP is available as a sterile lyophilized powder as follows:

C22110 10 mL single-dose vials containing vancomycin hydrochloride equivalent to 500 mg vancomycin base. Flip-top vials in packages of 25.


C28420 20 mL single-dose vials containing vancomycin hydrochloride equivalent to 1 g vancomycin base. Flip-top vials in packages of 10.

Pharmacy Bulk Packages:

C295B1 100 mL single use vials containing vancomycin hydrochloride equivalent to 5 g vancomycin base. Flip-top vial individually packaged.

C314061 100 mL single use vials containing vancomycin hydrochloride equivalent to 10 g vancomycin base. Flip-top vial individually packaged.

PHARMACEUTICAL PARTNERS OF CANADA INC.
Richmond Hill, ON L4B 3P6

 1-877-821-7724