PRODUCT MONOGRAPH

[Pr]Sterile Vancomycin Hydrochloride, USP

[Pr]Vancomycin Hydrochloride for Injection, USP

Antibiotic

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Date of Preparation:
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Control No.: 119199

NAME OF DRUG

Sterile Vancomycin Hydrochloride, USP
Vancomycin Hydrochloride for Injection, USP

THERAPEUTIC CLASSIFICATION

ANTIBIOTIC

ACTION

In vitro studies indicate that the bactericidal action of vancomycin hydrochloride against many gram-positive bacteria results from the inhibition of cell-wall synthesis. There is also evidence that vancomycin alters the permeability of the cell membrane and selectively inhibits RNA synthesis.

INDICATIONS AND CLINICAL USES

VANCOMYCIN HYDROCHLORIDE IV may be indicated in the therapy of severe or life-threatening staphylococcal infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins or who have infections with staphylococci resistant to other antibiotics, including methicillin.

VANCOMYCIN HYDROCHLORIDE IV has been used successfully alone in the treatment of staphylococcal endocarditis.

VANCOMYCIN HYDROCHLORIDE IV has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus viridans* or *S. bovis.* For endocarditis caused by enterococci (e.g. *E. faecalis*), VANCOMYCIN HYDROCHLORIDE IV has been reported to be effective only in combination with an aminoglycoside.

VANCOMYCIN HYDROCHLORIDE IV has been reported to be effective for the treatment of diphtheroid endocarditis. VANCOMYCIN HYDROCHLORIDE IV 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 bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to VANCOMYCIN HYDROCHLORIDE IV.

Its effectiveness has been documented in other infections due to staphylococci, including osteomyelitis, pneumonia, septicemia, and soft-tissue infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Although no controlled clinical efficacy trials have been conducted, VANCOMYCIN HYDROCHLORIDE IV, has been suggested by the American Heart Association and the American Dental Association for 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).

CONTRAINDICATION

VANCOMYCIN HYDROCHLORIDE is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Rapid bolus administration (e.g. over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest.

When given intravenously, toxic serum levels can occur. Vancomycin is excreted fairly rapidly by the kidney and blood levels increase markedly with decreased renal clearance.During parenteral therapy, the risk of toxicity appears appreciably increased by high blood concentrations or prolonged treatment. VANCOMYCIN HYDROCHLORIDE is poorly absorbed orally. Toxic serum levels are therefore not attained from oral dosage.

Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate in these patients.

Ototoxicity has occurred when serum levels exceeded 80 μg/mL. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience

with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic agents, particularly ethacrynic acid, neuromuscular blocking agents, aminoglycoside antibiotics, polymixin B, colistin, viomycin, and cisplatin, requires careful monitoring.

If parenteral and oral vancomycin are administered concomitantly an additive effect can occur. This should be taken into consideration when calculating the total dose. In this situation serum levels of the antibiotic should be monitored.

PRECAUTIONS

VANCOMYCIN HYDROCHLORIDE IV should be administered in a dilute 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 (See Dosage and Administration and Adverse Reactions).

Because of its ototoxicity and nephrotoxicity, VANCOMYCIN HYDROCHLORIDE should be used with care in patients with renal insufficiency. If it is necessary to use VANCOMYCIN HYDROCHLORIDE parenterally in patients with renal impairment, the dose and/or dose intervals should be adjusted carefully and blood levels monitored.

VANCOMYCIN HYDROCHLORIDE should be avoided (if possible) in patients with previous hearing loss. If it is used in such patients, the dose of VANCOMYCIN HYDROCHLORIDE should be regulated by periodic determination of drug levels in the blood. Patients with renal insufficiency and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic hematologic studies, urinalyses, and liver and renal function tests.

The prolonged use of VANCOMYCIN HYDROCHLORIDE may result in overgrowth of non-susceptible organisms. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken, including withdrawal of VANCOMYCIN HYDROCHLORIDE. In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who receive intravenous vancomycin.

Since VANCOMYCIN HYDROCHLORIDE IV is irritating to tissue and causes drug fever, pain and possibly necrosis it should *never* be injected intramuscularly; it must be administered intravenously. Pain and thrombophlebitis occur in many patients receiving VANCOMYCIN HYDROCHLORIDE IV and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized if the drug is administered in a volume of at least 200 mL of glucose or saline solution and if the sites of injection are rotated.

There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of VANCOMYCIN HYDROCHLORIDE IV as a 60-minute infusion prior to anesthetic induction.

The safety and efficacy of VANCOMYCIN HYDROCHLORIDE IV administration 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, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances 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.

In vitro resistance to Vancomycin has been reported among some enterococcal and staphylococcal isolates.

Usage in Pregnancy: VANCOMYCIN HYDROCHLORIDE should be given to a pregnant woman only if clearly needed. In a controlled clinical study, VANCOMYCIN HYDROCHLORIDE was administered to 10 pregnant women for serious staphylococcal infections complicating intravenous drug abuse to evaluate potential ototoxic and nephrotoxic effects on the infant. VANCOMYCIN HYDROCHLORIDE levels of 13.2 and 16.6 μg/mL were measured in cord blood of two patients. No sensorineural hearing loss or nephrotoxicity attributable to VANCOMYCIN HYDROCHLORIDE was noted. One infant whose mother received VANCOMYCIN HYDROCHLORIDE in the third trimester experienced conductive hearing loss that was not attributed to the administration of

VANCOMYCIN HYDROCHLORIDE. Because the number of patients treated in this study was limited and VANCOMYCIN HYDROCHLORIDE was administered only in the second and third trimesters, it is not known whether VANCOMYCIN HYDROCHLORIDE causes fetal harm.

Nursing Mothers: VANCOMYCIN HYDROCHLORIDE is excreted in human milk. Caution should be exercised if VANCOMYCIN HYDROCHLORIDE is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue administration of the drug, taking into account the importance of the drug to the mother.

Usage in Pediatrics: 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 children.

Geriatrics: The natural decrease 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.

ADVERSE REACTIONS

Infusion-related Events: During or soon after rapid infusion of VANCOMYCIN HYDROCHLORIDE IV, patients may develop anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, or pruritis. Rapid infusion may also cause flushing of the upper body ("red neck") 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 HYDROCHLORIDE IV is given by slow infusion over 60 minutes. In studies in normal volunteers, infusion-related events did not occur when VANCOMYCIN HYDROCHLORIDE IV 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 HYDROCHLORIDE, 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 pre-existing kidney dysfunction. When VANCOMYCIN HYDROCHLORIDE was discontinued, azotemia resolved in most patients.

Ototoxicity: A few dozen cases of hearing loss associated with VANCOMYCIN HYDROCHLORIDE have been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or 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 HYDROCHLORIDE or after a total dose of more than 25 g, has been reported in several dozen patients. Neutropenia appears to be promptly reversible when VANCOMYCIN HYDROCHLORIDE is discontinued. Thrombocytopenia has rarely been reported. Although a causal relationship has not been established, reversible agranulocytosis (granulocyte count less than 500/mm^3) has been reported rarely.

Phlebitis: Inflammation at the injection site has been reported.

Miscellaneous: Anaphylaxis, drug fever, nausea, chills, eosinophilia, hypotension, wheezing, dyspnea, urticaria, pruritus flushing of the upper body ("red neck"), pain and muscle spasm of the chest and back, rashes, including exfoliative dermatitis, Stevens-Johnson syndrome, linear IgA bullous dermatosis and rare cases of vasculitis have been associated with the administration of VANCOMYCIN HYDROCHLORIDE.

TREATMENT OF OVERDOSAGE

Other than general supportive treatment, no specific antidote is known. Dialysis does not remove significant amounts of vancomycin. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

Dosage

Intravenous:

Adults

The usual intravenous dose is 500 mg every six hours or 1 g every twelve hours.

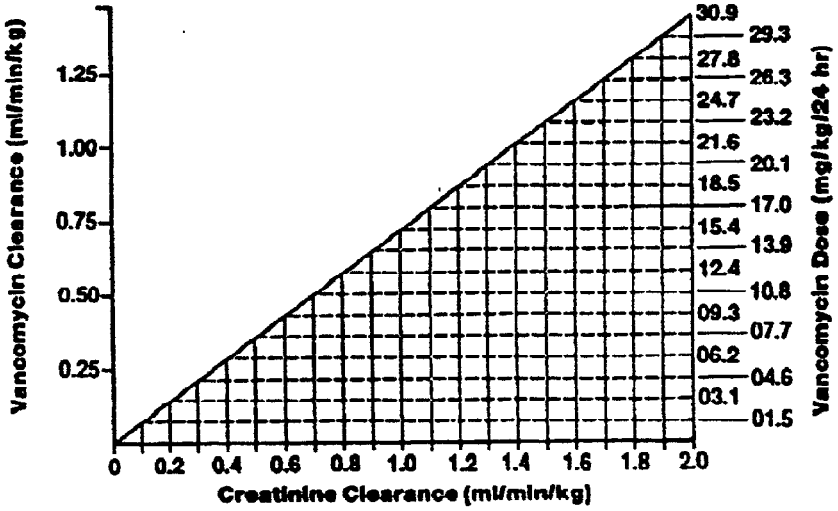
Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Adults with Impaired Renal Function:

Dosage adjustment must be made in patients with impaired renal function to avoid toxic serum levels. Serum levels should be checked regularly, since accumulation in such patients has been reported to occur over several weeks of treatment.

For most patients with renal impairment or the elderly, the dosage calculation may be made by using the following nomogram[1] if the creatinine clearance value is known.

Figure 1: Nomogram Relating Vancomycin Clearance, Creatinine Clearance and Vancomycin Dose



1. Moellering, R.C., *et al*.: Vancomycin Therapy in Patients with Impaired Renal Function: A Nomogram for Dosage, Ann. Int. Med., 1981, 94:343.

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

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into estimated creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/dL)}}$

Females: 0.85 x above value

In anuria, a dose of 1 g every 7 to 10 days has been recommended.

Neonates, Infants and Children

The following dosage schedule has been used. Infusions should be over 60 minutes, and can be divided and incorporated in the child's 24-hour fluid requirement.

Infants and Neonates

In both neonates and infants it is suggested that an initial dose of 15 mg/kg be given followed by 10 mg/kg every 12 hours for neonates in the first week of life and every 8 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 warranted in these patients.

Children

The usual intravenous dosage of VANCOMYCIN HYDROCHLORIDE is 10 mg/kg per dose given every 6 hours. The majority of patients with infections caused by organisms susceptible to the antibiotic show 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 3 weeks or longer is recommended.

Administration

Intermittent Intravenous Infusion: The reconstituted solution must be FURTHER DILUTED with 100-200 mL Normal Saline or 5% Dextrose in Sterile Water for Injection. This should be infused over a period of at least 60 minutes.

See instructions in the **Reconstitution** section.

Continuous Intravenous Infusion: Should be used only when intermittent infusion is not practical.

Note: Infusion-related events are related to both concentration and rate of administration of vancomycin. Concentration of no more than 5 mg/mL and rates of no more than 10 mg/min are recommended in adults (see age-specific recommendations). 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 risk of infusion-related events. Infusion related events may occur, however, at any rate or concentration.

Note: VANCOMYCIN HYDROCHLORIDE capsules are formulated in a matrix gel that prevents administration by a nasogastric tube; if this route of administration is being considered, the IV dosage form should be used.

PHARMACEUTICAL INFORMATION

Chemistry

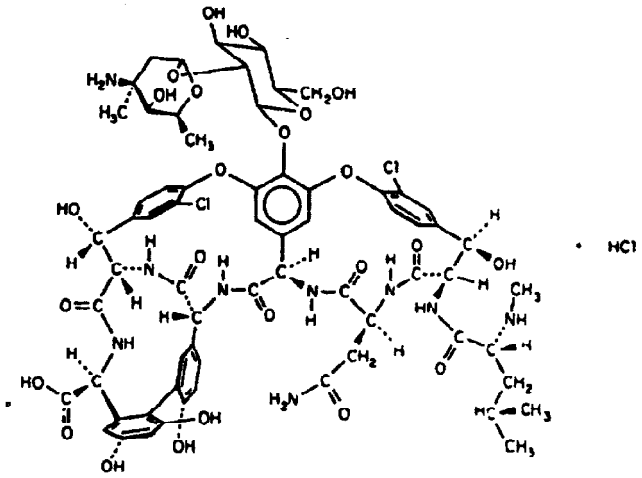
Trade Name: STERILE VANCOMYCIN HYDROCHLORIDE

Proper Name: Vancomycin hydrochloride

Chemical Name:

(S_a)-(3S,6R,7R,22R,23S,26S,36R,38aR)-44-[[2-0-(3-Amino-2,3,
6-trideoxy-3-C-methyl-α-L-lyxo-hexopyranosyl)-β-D-glucopyrano-
syl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,
25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-
[(2R)-4-methyl-2-(methylamino)valeramido]-2,5,24,38,39-pentaoxo-
22H-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-
dimetheno-1H,16H-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16] -benzoxadiazacyclo
-tetracosine-26, carboxylic acid, monohydrochloride

Structure:



Mol. Formula: $C_{66}H_{75}Cl_2N_9O_{24}.HCl$

Mol. Weight: 1485.68

Description: Vancomycin hydrochloride, is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). It is an off-white free flowing powder, having essentially no odor. It is soluble in water and insoluble in organic solvents.

Composition

STERILE VANCOMYCIN HYDROCHLORIDE vials for IV use, contain vancomycin hydrochloride (expressed in terms of free base) as a lyophilized plug. When reconstituted in water, it forms a clear, colourless solution with a pH range of 2.5 to 4.5.

RECONSTITUTION

Solution for Reconstitution

Sterile Water for Injection USP

Reconstitute as follows:

Table 1: Reconstitution Table

Vial Size	Volume to be Added to Vial	Approximate Available Volume	Approximate Average Vancomycin Concentration
500 mg	10 mL	10.3 mL	50 mg/mL
1.0 g	20 mL	20.6 mL	50 mg/mL

Shake well until dissolved.

Note: Further Dilution is Required.

Note: Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution or container permits.

For Intermittent Intravenous Infusion

500 mg vial: Reconstituted solutions must be diluted with at least 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose in Sterile Water for Injection.

1 g vial: Reconstituted solutions must be diluted with at least 200 mL of 0.9% Sodium Chloride Injection or 5% Dextrose in Sterile Water for Injection.

For Continuous Intravenous Infusion

The vials reconstituted according to the above table should be further diluted to the desired volume with any of the solutions for IV infusion listed below.

Solutions for IV Infusion

5% Dextrose Injection
5% Dextrose Injection and 0.9% Sodium Chloride Injection
Lactated Ringer's Injection
Lactated Ringer's in 5% Dextrose Injection
Normosol®-M in D5-W
0.9% Sodium Chloride Injection
Isolyte® E
Acetated Ringer's Injection

Pharmacy Bulk Vial

THE AVAILABILITY OF THE BULK PHARMACY VIAL IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

VANCOMYCIN HYDROCHLORIDE FOR INJECTION does not contain any preservatives. The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture.

Table 2: Reconstitution Table

Vial Size	Volume to be Added to Vial	Approximate Available Volume	Approximate Average Vancomycin Concentration
10 g	95 mL	100 mL	100 mg/mL

Note: Reconstitute with Sterile Water for Injection.

Use reconstituted stock solution within 8 hours, and further diluted solutions within 24 hours if kept at room temperature and 96 hours if refrigerated from time of initial puncture.

STABILITY AND STORAGE RECOMMENDATIONS

Dry Powder

Store between 15 and 25° C.

Solutions

Reconstituted stock solution for Pharmacy Bulk vials should be used within 8 hours. All other reconstituted solutions and further diluted infusion mixtures should be used within 24 hours if kept at room temperature or 96 hours when refrigerated.

Incompatibility

Vancomycin solution has a low pH that may cause physical or chemical instability when it is mixed with other compounds. Mixing with alkaline solutions should be avoided.

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 adequately flush the intravenous lines between the administration 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.

Some of the specific substances found incompatible are aminophylline, chloramphenicol sodium succinate, dexamethasone phosphate, diphenylhydantoin

sodium, methicillin, vitamin B_{12} complex with C, sulfisoxazole diethanolamine, heparin sodium, potassium penicillin G,

hydrocortisone sodium succinate, amobarbital sodium, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, sodium bicarbonate, and sulfadiazine sodium.

Note: Common flavouring syrups have been added to the solution to improve the taste for oral administration. There is no information to indicate that the potency or efficacy of the drug is affected by the addition of these agents.

AVAILABILITY OF DOSAGE FORMS

STERILE VANCOMYCIN HYDROCHLORIDE is available as a sterile lyophilized powder in vials containing vancomycin hydrochloride equivalent to 500 mg and 1 g vancomycin base.

VANCOMYCIN HYDROCHLORIDE FOR INJECTION Pharmacy Bulk Vial 7355 is available in vials containing vancomycin hydrochloride equivalent to 10 g vancomycin base, edetate calcium disodium equivalent to 0.2 mg edetate/g vancomycin, and ethanol equivalent to up to 30 mg/g vancomycin.

MICROBIOLOGY

Cross-resistance has not been demonstrated between VANCOMYCIN HYDROCHLORIDE and other classes of antibiotics. Laboratory-induced resistance has been reported to occur in a slow stepwise fashion. The development of resistance to vancomycin by staphylococci has not been reported in clinical use. Its activity is not significantly altered by changes in pH or by the presence of serum. Vancomycin is active against most strains of the following organisms *in vitro* and in clinical infections:

Staphylococcus aureus (including heterogeneous methicillin-resistant strains)
Clostridium difficile
S. epidermidis (including heterogeneous methicillin-resistant strains)
Streptococcus pneumoniae (including multiple-resistant strains)
S. pyogenes (group A beta-hemolytic)
S. agalactiae (group B beta-hemolytic)
S. bovis
Alpha-hemolytic *streptococci* (*viridans* groups)
Enterococci (e.g., *E. faecalis*)
Bacillus sp.
Listeria monocytogenes
Lactobacillus sp.
Neisseria sp.
Diphtheroids
Actinomyces sp.

Note: Many strains of *streptococci, staphylococci*, *C. difficile*, and other gram-positive bacteria are susceptible *in vitro* to concentrations of 0.5 to 5 μg/mL. *Staphylococci* are generally susceptible to less than 5 μg/mL of vancomycin hydrochloride, but a small proportion of *S. aureus* strains requires 10 to 20 μg/mL for inhibition.

In vitro resistance to Vancomycin has been reported among some enterococcal and staphylococcal isolates.

Vancomycin is not effective *in vitro* against gram-negative bacilli, mycobacteria, or fungi.

Table 3: *In Vitro* Activity of Vancomycin

Organism	No. of Strains	MIC (μg/mL) Range	Median
Staphylococcus aureus	55	1.0 - 2.0	1.0
	101	0.78 - 12.5	3.1
	35	0.25 - 1.0	1.0
Staphylococcus aureus (methicillin-resistant)	22	0.5 - 4.0	0.5
	38	0.3 - 12.0	1.5
	12	0.2 - 3.12	0.4
Streptococcus epidermidis	177	1.56 - 6.25	3.1
	35	0.4 - 3.1	1.6
	27	0.2 - 6.25	3.12
Streptococcus pneumoniae	70	0.125 - 0.5	0.25
Streptococcus pyogenes	12	0.8 - 3.1	1.6
Streptococcus viridans	82	0.39 - 1.56	0.78
Streptococcus group D *Enterococci*	382	0.8 -> 100.0	3.1
Clostridium perfringens	43	0.4 - 1.6	0.8
Clostridium ramosum	49	3.1 - 12.5	6.2
Clostridium difficile	14	<1.0	<1.0
	78	1.0 - 4.0	

Methods of Susceptibility Testing

When the standardized method of disc susceptibility testing is used, a 30 μg disc of vancomycin should produce a zone of *more than* 11 mm when in contact with "susceptible" organisms. A zone size of 10-11 mm indicates intermediate susceptibility, while a zone size of 9 mm or less indicates resistance.

With the WHO-ICS agar dilution and broth dilution methods, an MIC of ≤ 5 μg/mL indicates susceptibility to vancomycin.

Assay Methods

Vancomycin serum and tissue levels may be determined by Bennett's agar-well diffusion method. This test can quantitatively measure vancomycin concentrations from 0.5 to 8 μg/mL.

Two disc-diffusion assay methods are available for vancomycin. Both use *Bacillus subtilis* as the test organism. The first method, which uses antibiotic medium No. 5, is capable of measuring vancomycin levels from approximately 5 to 40 μg/mL. The second uses minimal salt agar and is capable of detecting vancomycin concentrations from about 0.8 to 25 μg/mL. A modification of this assay permits reliable bioassay for vancomycin (in concentrations of 0.78 to 50.0 μg/mL) in the presence of rifampin or aminoglycosides. Two commercially prepared assay methods are now available and include a radioimmunoassay and an automated fluorescence polarization immunoassay.

PHARMACOLOGY

HUMAN PHARMACOLOGY

Adults:

Intravenous Administration:

Vancomycin is 55% protein bound as measured by ultrafiltration at Vancomycin serum levels of 10 to 100 mg/L.

About 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration in the first 24 hours. Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. Renal Vancomycin clearance is fairly constant and accounts for 70% to 80% of Vancomycin elimination. When a single intravenous injection of 500 mg of vancomycin was administered over 30 minutes to healthy volunteers, the mean serum peak concentration was 51 μg/mL, 18.6 μg/mL at 1 hour and 5.8 μg/mL at 6 hours post infusion. After a 1 g single dose I.V. over 30 minutes, the mean peak level was 85 μg/mL, 29 μg/mL at 1 hour, 11 μg/mL at 6 hours, and 5.1 μg/mL at 12 hours post infusion. Following multiple dosages of 500 mg every 6 hours infused over 30 minutes, the mean peak ranged from 41-57 μg/mL. Following multiple 60 minute 1 g I.V. infusions of vancomycin in healthy volunteers, mean peak plasma concentrations were 64 μg/mL, 12.5 μg/mL at 6 hours, and 7 μg/mL at 12 hours post

infusion. The plasma half-life ranged from 3 to 8 hours with an overall mean of 4.5 hours.

There is no apparent metabolism of the drug.

Renal Insufficiency:
Infusions of 1 g vancomycin in 250 mL D5-W were given over 30 minutes to 29 anephric patients. After 18 days with intermittent dialysis at three-day intervals, the serum concentration was still 3.5 μg/mL. The elimination half-life was about 7.5 days.

Tissue Penetration and Distribution:
Central Nervous System: Vancomycin does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

Other Tissues and Fluids: Vancomycin concentration in human pericardial, pleural, bile, ascitic and synovial fluids reaches approximately one third of the equivalent serum level after single intravenous doses. A level of 7.6 μg/mL was achieved in the brain cyst of one infant following intravenous infusion of 40 mg/kg daily for 4 days.

TOXICOLOGY

Acute Toxicity

Vancomycin was administered to mice, rats and dogs by various routes.

Table 4: $LD_{50} \pm SE$ (mg/kg) following Vancomycin

Route of Administration	Rat	Mouse	Dog
Intravenous	319 ± 14	489 ± 41	292 ± 29
Intraperitoneal	2218 ± 240	1734 ± 227	
Subcutaneous		> 5000	
Oral		> 5000	

Rats died quickly from CNS-mediated effects, while dogs died, generally from kidney failure, several days after the intravenous administration.

Vancomycin, when administered intravenously in a 5 percent solution to dogs at a rate of 0.6 mL/minute, caused a slight dose-related drop in blood pressure. When the same dogs were given the same doses at a rate of 15 mL/minute, blood pressure dropped dramatically, as much as 40 percent. Whether the response is due to a direct effect on histamine receptors or to release of histamine, possibly from mast cells, is not known.

Subchronic Toxicity

Dogs were given daily i.v. doses of vancomycin at 12.5 mg and 50 mg/kg for 21-311 days. Renal damage was seen in 4/22 dogs receiving 50 mg/kg/day.

Monkeys tolerated i.v. doses of 25 and 50 mg/kg/day for 16-187 days, with irritation at the injection site as the only toxic effect.

Cats received i.v. doses of 25 and 50 mg/kg/day for three months with no systemic toxicity.

Anaphylaxis could not be induced in 9 guinea pigs that received 100 mg vancomycin subcutaneously when challenged by a 25 mg i.v. dose, 25 days later.

Intraperitoneal doses of 150 mg vancomycin or 60 mg tobramycin given subcutaneously to rats, resulted in no nephrotoxicity; however, when administered together, significant renal toxicity occurred.

Vancomycin 1000 mg/kg administered subcutaneously concurrently with ethacrynic acid 40 mg/kg intravenously, did not produce ototoxicity in a guinea pig model.

Neuromuscular blocking has not been demonstrated in vancomycin-treated rabbits.

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