Vancomycin is an antibiotic isolated from strains of *Streptomyces orientalis*. It was introduced in 1956 for the treatment of penicillin-resistant staphylococci. Due to the toxicity of the original preparation (known affectionately as "Mississippi Mud") and the introduction of the penicillinase-resistant penicillins, vancomycin usage declined substantially in 1960s. However, with purification of the preparation, increased understanding of its pharmacokinetics in renal disease and the emergence of methicillin-resistant staphylococci, vancomycin has enjoyed a renewed interest.

**Mechanism of Action**

Vancomycin inhibits the synthesis of cell wall phospholipids and peptidoglycan polymers. The synthesis of RNA is also inhibited and vancomycin may alter the permeability of the cytoplasmic membranes of protoplasts.

**Antimicrobial Spectrum of Activity**

Vancomycin exerts antimicrobial activity in vitro against most gram-positive cocci and bacilli: *Staphylococcus aureus*, coagulase-negative staphylococci, *Strep. pyogenes*, *Strep. agalactia*, *Strep. pneumoniae*, *Strep. viridans*, *Strep. bovis*, enterococci, anaerobic and microaerophilic streptococci, *Clostridium*, *Bacillus anthracis*, *Actinomycosis*, *Listeria*, *JK diphtheroids* and *Corynebacterium diphtheriae*. A minimum inhibitory concentration of < 5 mcg/ml indicates susceptibility to vancomycin. For the majority of organisms, there is little difference between inhibitory and bactericidal concentrations. Notable exceptions to this include enterococci, *Strep. viridans* and *Strep. bovis*. There is no report of cross-resistance between vancomycin and other antibiotics and resistance rarely develops during therapy despite of 25 years of clinical experience. However there is at least one report of a strain of vancomycin-resistant *Staph. aureus*, which was selected by passage in the presence of subinhibitory concentrations of the drug in vitro. Enhanced antimicrobial activity has been demonstrated in combination with aminoglycosides against *Staph. aureus*, *Strep. bovis*, *Strep. viridans* and enterococci.

Vancomycin lacks in vitro activity against Enterobacteriaceae, Pseudomonadaceae and other gram-negative bacteria including *Legionella* species. Mycobacteria, fungi and viruses are also resistant.

**Pharmacokinetics**

Vancomycin is poorly absorbed from the GI tract and therapeutic plasma concentrations are unlikely even in the presence of inflamed gut or end-stage renal disease (ESRD). However, a recently reported case demonstrated substantial plasma concentrations in a patient with pseudomembranous colitis and anuric renal failure. High fecal concentration (up to 400 mcg/ml) has been noted after oral ingestion of 125 mg every six hours.

Serum vancomycin concentrations follow a 2 or 3 compartment model after intravenous administration. Administration of a single 10 mg/kg dose over 30 minutes produces mean serum concentration of approximately 15 mcg/ml. 30 to 45 minutes post-infusion. Accumulation will occur after repetitive dosing. Clearance of vancomycin is linearly related to creatinine clearance. The majority of drug is excreted unchanged in the urine via glomerular filtration. Serum half-lives are typically 6-8 hours with normal renal function and extend to 200-250 hours in ESRD. Hemodialysis can increase the clearance of vancomycin some what, and the need for post-dialysis dosing will depend on the duration of dialysis. Intermittent peritoneal dialysis will depend on the duration of dialysis. Intermittent peritoneal dialysis can result in therapeutic peritoneal fluid concentrations. However, intermittent peritoneal dialysis does not substantially alter clearance. Administration of vancomycin in continuous ambulatory peritoneal dialysis fluid (4-6 hour dwell time) allows for substantial absorption and therapeutic plasma concentrations. A small amount of the drug is excreted in the bile.
Hepatic dysfunction has been reported to prolong the half-life of vancomycin. Vancomycin penetration into the CSF is negligible in normal subjects and unreliable in adult patients with meningitis. In some children, CSF concentrations sufficient for effective therapy are attained with parenteral therapy. It readily diffuses into pleural, pericardial, ascitic and synovial fluids following standard parenteral therapy.

**Indications for use**

Vancomycin should be considered for

1. serious staphylococcal infections in patients intolerant to penicillins and cephalosporins
    - patients infected with organisms resistant to penicillins and cephalosporins ie. methicillin resistant staphylococci
2. serious streptococcal infections in patients intolerant to penicillins and cephalosporins
    - patients infected with organisms resistant to penicillins eg. penicillin resistant pneumococci.

Vancomycin should be combined with aminoglycoside (eg. gentamicin) for the treatment of serious enterococcal infection eg. enterococcal infective endocarditis.

3. antibiotic associated diarrhea due to *Clostridium difficile* toxin.

4. prophylaxis (surgical wound and endocarditis) in penicillin allergic patients

**Dosage and Administration**

For systemic infections, vancomycin must be administered intravenously, since no satisfactory intramuscular preparation is available. Vancomycin should be diluted with D5W or normal saline in a concentration of no greater than 500 mg/100 ml and administered at a rate not exceeding 500 mg/30 minutes. If adverse reactions appear during the infusion, further dilution and prolongation of the administration time may be helpful. The suggested dosage regimen is 10 to 15 mg/kg every 8 to 12 hours for patient with normal renal function. Dosage adjustment is mandatory in patients with impaired renal function and the dosage nomogram is shown in Figure 1. Satisfactory serum concentrations are 30 to 40 mcg/ml for peak and 5 to 10 mcg/ml for trough.

For the treatment of *Clostridium difficile* colitis, vancomycin 125 mg orally every 6 hours is adequate. Vancomycin can be administered locally. Meningitis or intracranial shunt infection refractory to intravenous therapy requires small doses of vancomycin (5 to 20 mg per day) intrathecally or intraventricular injection. Peritonitis caused by methicillin-resistant *Staph. aureus* or coagulase negative staphylococcal strains in patients on peritoneal dialysis may be treated by intraperitoneal vancomycin; the drug should be added to the dialysis fluid at a concentration of 50 mg/l.

**Adverse Reactions and Toxicity**

The current purified product of vancomycin offers less side effects than the original preparations which contained up to 20 per cent of an unknown adulterant responsible for many of side effects encountered. The most common adverse effects of intravenous vancomycin include: phlebitis, fever, chills, pruritis, tachycardia, erythema, rash and red neck syndrome-tingling and flushing of the face and thorax. These reactions along with hypotension may be related to the rapidity of infusion and adequate drug dilution (5 mg/ml) and proper administration (over 30 to 60 minutes) minimize the frequency of vancomycin-associated reactions. Reversible neuropenia, eosinophilia and interstitial nephritis have also been reported. Otoxicity of tinnitus and high frequency hearing loss has been reported with elevated serum concentrations. Avoidance of excessively high serum concentrations may reduce the incidence of clinically detectable hearing deficits. A retrospective study of 100 courses of vancomycin revealed the following incidence of adverse reactions: phlebitis 13 per cent, rash 3 per cent, reversible neuropenia 2 per cent and reversible tinnitus 1 per cent. The incidence of nephrotoxicity (> 0.5 mg/dl increase in serum creatinine) in patients not receiving aminoglycoside was 5 per cent. All patients with nephrotoxicity had markedly elevated vancomycin trough concentrations. In the evaluable patients receiving vancomycin plus aminoglycoside, 35 per cent demonstrated nephrotoxicity. However many patients experiencing nephrotoxicity had elevated trough concentrations.
and no information was provided on the patients aminoglycoside dosing or serum concentrations. Oral vancomycin has an unpleasant taste and may cause nausea and vomiting.

LITERATURE CITED