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Vancomycin

Updated: December 1, 2013.

OVERVIEW

Information

Vancomycin is a broad spectrum antibiotic that has activity against methicillin-resistant strains of Staphylococcus aureus and is generally reserved for serious drug resistant gram-positive infections. Vancomycin therapy has been linked many to instances of hypersensitivity with fever, rash and eosinophilia that can be associated with mild hepatic injury, but despite over 50 years of use, it has not been linked to cases of serious hepatotoxicity.

Background

Vancomycin (van" koe mye' sin) is a glycopeptide antibiotic produced by Streptococcus orientalis with primary activity against gram positive bacteria. Vancomycin has a large, complex and unusual structure and is believed to act by inhibition of bacterial cell wall synthesis via binding to the cell wall precursor molecules. Vancomycin is active against, and its major use is in therapy of, infections due to methicillin-resistant Staphylococcus aureus (MRSA), including antibiotic-induced pseudomembranous colitis, staphylococcal enterocolitis, bacterial endocarditis, and sepsis. For systemic infections, vancomycin is given intravenously. For localized or nonsystemic infections, other routes of administration are used, including oral, rectal, topical, inhalational, intrathecal, intraperitoneal, and intraventricular. The recommended parenteral dosage in adults is 500 mg iv every 6 hours or 1000 mg every 12 hours, with modification to achieve a therapeutic range as needed. The recommended oral dosage in the treatment of antibiotic induced pseudomembranous enterocolitis is 125 to 500 mg every 6 hours for 7 to 10 days. Vancomycin is available generically and under several commercial names including Vancoled, Vancor, Lyphocin, and Vancocin in 125 and 250 mg pulvules and as power for injection or oral administration. Vancomycin was first approved for use in the United States in 1958 and it continues to be widely used, particularly with the recent rise in incidence of serious MRSA infections. Vancomycin is largely well tolerated; common side effects include diarrhea, nausea, nephrotoxicity and neutropenia.

Hepatotoxicity

Intravenous vancomycin is associated with minor, transient and asymptomatic elevations in serum aminotransferase levels in 1% to 5% of patients, but similar or minimally lower rates of abnormalities are usually reported with comparative agents. In rare instances, the serum enzyme elevations are more marked and may be associated with mild symptoms, although usually without jaundice. In recent years, vancomycin has been linked to hypersensitivity reactions, including Stevens Johnson syndrome, toxic epidermal necrolysis and the distinctive syndrome of drug rash, eosinophilia and systemic symptoms (DRESS). These forms of hypersensitivity generally arise within a few days to 3 to 4 weeks after initiation of intravenous (iv) vancomycin therapy. Fever and severe

skin rash generally dominate the clinical presentation, but systemic symptoms can include renal, respiratory or heart failure, neutropenia, thrombocytopenia, and mild liver injury. Cases of DRESS syndrome associated with vancomycin are often accompanied by serum enzyme elevations, but marked elevations, symptoms and jaundice are rare. Nevertheless, instances of death with hepatic failure have been described, although the features of hypersensitivity are usually more prominent than the liver injury. In addition, patients who received intravenous vancomycin usually have multiple comorbidities including sepsis, and receive multiple antibiotics making the association of the hypersensitivity reaction and liver injury with vancomycin sometimes difficult. Other more well known causes of DRESS syndrome include allopurinol, sulfonamides, and the aromatic anticonvulsants. These other causes of DRESS syndrome are more likely to be associated with clinically apparent and even fatal liver injury.

Mechanism of Injury

Vancomycin is rapidly excreted in the urine without significant hepatic metabolism, which perhaps explains the absence of significant hepatotoxicity. Hypersensitivity probably accounts for the instances of mild anicteric hepatitis associated with DRESS syndrome and Stevens Johnson syndrome due to iv vancomycin. The association of ALT elevations with oral vancomycin is surprising in view of its lack of oral absorption, but the presence of active colitis may allow for some systemic exposure.

Outcome and Management

In published cases, the hepatic injury has usually been self-limited, but rare instances of acute liver failure in the context of hypersensitivity reactions have been linked to vancomycin therapy. Vancomycin should be discontinued promptly in patients who develop immunoallergic features. Corticosteroids are often used to treat the systemic hypersensitivity and relapse is common when they are discontinued early. In general, recovery is usually slow despite early discontinuation of vancomycin. There is no evidence for cross sensitivity to hypersensitivity reactions to vancomycin with other antibiotics, except for teicoplanin, a vancomycin-like antibiotic available in some countries, but not the United States.

Drug Class: Antiinfective Agents

Other Drugs in the Subclass, Glycopeptide Antibiotics: Dalbavancin, Oritavancin, Telavancin,

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vancomycin – Generic, Vancocin®

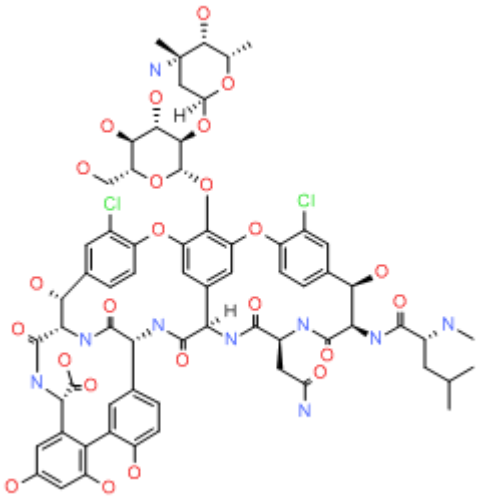
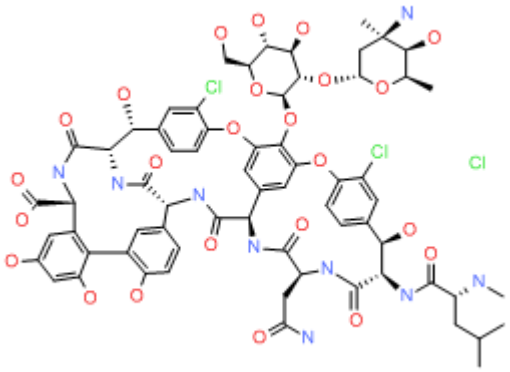
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Vancomycin	1404-90-6	C66-H75-C12-N9-O24	
Vancomycin Hydrochloride	1404-93-9	C66-H75-C12-N9-O24.Cl-H	

ANNOTATED BIBLIOGRAPHY

References updated: 01 December 2013

Zimmerman HJ. Hepatic injury from antimicrobial agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, p. 592.

(Expert review of liver injury published in 1999; does not mention vancomycin).

Moseley RH. Vancomycin. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 469.

(Expert review of antibiotic induced liver injury mentions that a single case report of vancomycin causing ALT elevations has been published).

MacDougall C, Chambers HF. Vancomycin. Protein synthesis inhibitors and miscellaneous antibacterial agents. In, Brunton LL, Chabner KA, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1539-42.

(Textbook of pharmacology and therapeutics).

Farber BF, Moellering RC Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob Agents Chemother 1983; 23: 138-41. PubMed PMID: 6219616.

(Analysis of 100 courses of iv vancomycin in 98 patients; fever and rash occurred in 3%, phlebitis 13%, neutropenia 2%, nephrotoxicity 5%, ototoxicity 0%, creatinine rise 35%; no mention of hepatotoxicity or ALT elevations).

Thompson CM Jr, Long SS, Gilligan PH, Prebis JW. Absorption of oral vancomycin - possible associated toxicity. Int J Pediatr Nephrol 1983; 4: 1-4. PubMed PMID: 6853034.

(Low levels of vancomycin were detected in serum of an anephric child given drug orally for Clostridium difficile pseudomembranous colitis).

Sorrell TC, Collignon PJ. A prospective study of adverse reactions associated with vancomycin therapy. J Antimicrob Chemother 1985; 16: 235-41. PubMed PMID: 3934126.

(Prospective analysis of 54 courses of iv vancomycin given for 4-49 days; rash occurred in 6%, phlebitis 37%, neutropenia 0%, nephrotoxicity 8%, ototoxicity 0%, creatinine rise 50%; slight bilirubin rise in 1 patient; no mention of ALT elevations).

Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet 1986; 11: 257-82. PubMed PMID: 3530582.

(Extensive review of clinical pharmacology of vancomycin; major adverse events are renal toxicity and ototoxicity, skin rash, thrombophlebitis and fever; no mention of liver-related toxicity).

Wilhelm MP. Vancomycin. Mayo Clin Proc 1991; 66: 1165-70. PubMed PMID: 1943250.

(Extensive review of vancomycin pharmacology, clinical efficacy and adverse events; no mention of hepatotoxicity).

Hauben M, Adler C. Acute hepatitis, interstitial nephritis, and eosinophilia. Ann Intern Med 1995; 122: 555-6. PubMed PMID: 7872595.

(35 year old woman with HIV infection developed acute rise in ALT [from 47 to 2374 U/L] and creatinine [from 0.8 to 7.6 mg/dL] and eosinophilia with no mention of jaundice, within 4 days of starting vancomycin and aztreonam; values improved after stopping, but were still abnormal 7 days later; patient also received a day of erythromycin).

Alexander II, Greenberger PA. Vancomycin-induced Stevens-Johnson syndrome. Allergy Asthma Proc 1996; 17: 75-8. PubMed PMID: 8934797.

(36 year old man developed Stevens-Johnson syndrome after 17 days of iv vancomycin, requiring switch to piperacillin and gentamicin with accompanying mild liver injury thereafter [AST 198 U/L, Alk P 232 U/L but no jaundice]; Stevens-Johnson syndrome responded to corticosteroids).

Martí R, Rosell M, Pou L, García L, Pascual C. Influence of biochemical parameters of liver function on vancomycin pharmacokinetics. Pharmacol Toxicol 1996; 79: 55-9. PubMed PMID: 8878246.

(Retrospective analysis of 76 patients treated with vancomycin revealed no liver abnormalities).

Elting LS, Rubenstein EB, Kurtin D, Rolston KVI, Fangtang J, Martin CG, Raad II, et al. Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. Cancer 1998; 83: 2597-607. PubMed PMID: 9874468.

(765 cancer patients were treated with vancomycin; significant nephrotoxicity, but no hepatotoxicity was noted).

Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: resolution following cyclosporine treatment. Clin Nephrol 2005; 64: 155-8. PubMed PMID: 16114793.

(45 year old woman developed fever 34 days after starting vancomycin followed by rash and renal failure [bilirubin 2.4 mg/dL, ALT 462 U/L, Alk P 257 U/L], treated with prednisone with two relapses during recovery).

Yazganoglu KD, Ozkaya E, Ergin-Ozcan P, Cakar N. Vancomycin-induced drug hypersensitivity syndrome. J Eur Acad Dermatol Venereol 2005; 19: 648-50. PubMed PMID: 16164735.

(56 year old woman developed fever, rash, facial edema and eosinophilia [1396/µL] 20 days after starting vancomycin [bilirubin and Alk P not given, ALT 229 U/L], resolving after 2 months on corticosteroid therapy).

Cadle RM, Mansouri MD, Darouiche RO. Vancomycin-induced elevation of liver enzyme levels. Ann Pharmacother 2006; 40: 1186-9. PubMed PMID: 16720708.

(57 year old man with Clostridium difficile colitis and persistent diarrhea was treated with oral vancomycin on 5 occasions, developing progressively increasing elevations in ALT [~100-400 U/L] without symptoms or jaundice with each treatment; ALT returned to baseline after each course and vancomycin could not be detected in serum).

Kwon HS, Chang YS, Jeong YY, Lee SM, Song WJ, Kim HB, Kim YK, et al. A case of hypersensitivity syndrome to both vancomycin and teicoplanin. J Korean Med Sci 2006; 21: 1108-10. PubMed PMID: 17179696.

(50 year old man with cirrhosis developed fever, rash and eosinophilia [1605/µL] 18 days after starting iv vancomycin [liver test results not provided], resolving on stopping vancomycin, but recurring on intravenous teicoplanin [an antibiotic similar to vancomycin]).

Tamagawa-Mineoka R, Katoh N, Nara T, Nishimura Y, Yamamoto S, Kishimoto S. DRESS syndrome caused by teicoplanin and vancomycin, associated with reactivation of human herpesvirus-6. Int J Dermatol 2007; 46: 654-5. PubMed PMID: 17550572.

(52 year old woman developed fever, lymphadenopathy, rash, facial edema and eosinophilia [7%] a few days after starting iv vancomycin [bilirubin not provided, ALT 547 U/L, Alk P 2209 U/L], resolving once vancomycin was stopped and corticosteroids added; positive lymphocyte stimulation test to vancomycin and teicoplanin).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, vancomycin was not implicated in any case).

Vauthey L, Uçkay I, Abrassart S, Bernard L, Assal M, Ferry T, Djordjevic M, et al. Vancomycin-induced DRESS syndrome in a female patient. Pharmacology 2008; 82: 138-41. PubMed PMID: 18607115.

(60 year old woman developed fever, rash and facial edema 18 days after starting iv vancomycin [liver tests normal except for GGT of 224 U/L], resolving with corticosteroid therapy).

Mennicke M, Zawodniak A, Keller M, Wilkens L, Yawalkar N, Stickel F, Keogh A, et al. Fulminant liver failure after vancomycin in a sulfasalazine-induced DRESS syndrrome: fatal recurrence after liver transplantation. Am J Transplant 2009; 9: 2197-2202. PubMed PMID: 19706026.

(60 year old man developed fever, rash and eosinophilia 6 weeks after starting sulfasalazine [bilirubin 2.7 mg/dL, ALT 650 U/L, Alk P 181 U/L]; started on iv vancomycin and ALT rose to 6,745 U/L 2 days later; emergency liver transplantation was done, after which he developed rash, fever and liver injury again while on piperacilin/tazobactam and caspofungin, dying suddenly of hemorrhage).

Vinson AE, Dufort EM, Willis MD, Eberson CP, Harwell JI. Drug rash, eosinophilia, and systemic symptoms syndrome: Two pediatric cases demonstrating the range of severity in presentation--A case of vancomycin-induced drug hypersensitivity mimicking toxic shock syndrome and a milder case induced by minocycline. Pediatr Crit Care Med 2010; 11: e38-43. PubMed PMID: 20407399.

(14 year old boy developed fever and rash 3 weeks after starting iv vancomycin and worsened with continuation [ALT 92 rising to 436 U/L, bilirbin and Alk P not given, eosinophils 16%], responding to stopping drug and corticosteroids).

Chen Y, Yang XY, Zeckel M, Killian C, Hornbuckle K, Regev A, Voss S. Risk of hepatic events in patients treated with vancomycin in clinical studies: a systematic review and meta-analysis. Drug Saf 2011; 34: 73-82. PubMed PMID: 21142272.

(Systematic review of 20 controlled trials of iv vancomycin in 7419 patients, found rates of liver enzyme elevations ["hepatic events"] to be 1.8-1.9 times higher with vancomycin than with comparator arms; with vancomycin monotherapy rates were only 0.4% vs 0.3%, while with combination therapy rates were 6.8% vs 3.9%; no reports of clinically apparent liver disease with jaundice).

Schnetzke U, Bossert T, Scholl S, Freesmeyer M, Hochhaus A, La Rosée P. Drug-induced lymphadenopathy with eosinophilia and renal failure mimicking lymphoma disease: dramatic onset of DRESS syndrome associated with antibiotic treatment. Ann Hematol 2011; 90: 1353-5. PubMed PMID: 21298267.

(30 year old man developed fever, lymphadenopathy, atypical lymphocytosis, eosinophilia [25%] and acute renal failure while receiving several antibiotics including vancomycin [liver test results not given], resolving with corticosteroid therapy after stopping antibiotics).

O'Meara P, Borici-Mazi R, Morton AR, Ellis AK. DRESS with delayed onset acute interstitial nephritis and profound refractory eosinophilia secondary to Vancomycin. Allergy Asthma Clin Immunol 2011; 7: 16. PubMed PMID: 21968185.

(66 year old man developed rash 4 weeks after starting iv vancomycin therapy followed by fever [40 ^{o}C] and facial edema [bilirubin 0.8 mg/dL, ALT 144 U/L, GGT 354 U/L, eosinophils 3620/μL], with subsequent respiratory and renal failure, followed by a slow, but ultimately full recovery on corticosteroid therapy).

Fleming P, Marik PE. The DRESS syndrome: the great clinical mimicker. Pharmacotherapy 2011; 31: 332. PubMed PMID: 21361742.

(44 year old woman with tracheostomy, hemorrhagic stroke and sepsis developed fever, rash and eosinophilia [25%] several days after starting iv vancomycin [bilirubin 0.2 rising to 12.8 mg/dL, ALT 127 U/L, Alk P not provided], responding to corticosteroid therapy).

Tran NP, Katcher J, Rohman E, Hall MF, Michael CF, Miyairi I, Lew DB. Vancomycin hypersensitivity diagnosed by lymphocyte blast transformation. Case Rep Pediatr 2011; 2011: 562620. PubMed PMID: 22606516.

(15 year old male developed rash, fever and renal disease 8-10 days after starting vancomycin [eosinophils 980/μL, liver tests not provided], with positive lymphocyte stimulation test to vancomycin and resolution on switching to other antibiotics).

Blumenthal KG, Patil SU, Long AA. The importance of vancomycin in drug rash with eosinophilia and systemic symptoms (dress) syndrome. Allergy Asthma Proc 2012 ; 33: 165-71. PubMed PMID: 22525393.

(Among 6 cases of DRESS syndrome seen at a single referral hospital over an 18 month period, 5 arose 12 days to 4 weeks after starting iv vancomycin therapy with fever, rash and eosinophilia [bilirubin 1.8 mg/dL in one patient, ALT 75-347 U/L, Alk P 181-378 U/L], 4 had history of allergies, 3 were treated with corticosteroids, 2 had at least one relapse, and all ultimately resolved).

Müller PA, Amann K, Bröcker EB, Trautmann A. [Maculo-papular exanthem with acute renal failure. Drug-induced hypersensitivity syndrome]. Hautarzt 2012; 63: 223-5. German. PubMed PMID: 21971769.

(44 year old man developed fever, rash, eosinophilia [3601/μL] and renal injury 4 weeks after starting iv vancomycin [liver tests not provided], resolving with corticosteroid therapy).

Díaz-Mancebo R, Costero-Fernández O, Vega-Cabrera C, Olea-Tejero T, Yébenes L, Picazo ML, Selgas-Gutiérrez R. Dress syndrome and acute tubulointerstitial nephritis after treatment with vancomycin and beta-lactams. Case report and literature review. Nefrologia 2012; 32: 685-7. PubMed PMID: 23013963.

(74 year old woman developed rash, fever, eosinophilia and renal failure several weeks after starting vancomycin [ALT raised, values not given], with slow resolution on corticosteroid therapy).

Kitcharoensakkul M, Ree N, Bloomberg GR, Dehner LP, Heidingsfelder JA, White AJ, Cooper MA. Vancomycin-induced DRESS with evidence of T-cell activation in a 22-month-old patient. Ann Allergy Asthma Immunol 2012; 109: 280-1. PubMed PMID: 23010236.

(22 year old woman developed fever, rash and eosinophilia 17 days after starting iv vancomycin [hepatomegaly noted but no liver tests provided], improving on corticosteroid therapy, but dying suddenly 18 days after hospital discharge).

Dauby N, Fink W, Seyler L, Luce S, Nouwynck C, Tas S, Jacobs F. Probable hypersensitivity reaction to vancomycin associating rash, fever and neutropenia. Acta Clin Belg 2012; 67: 226-8. PubMed PMID: 22897075.

(54 year old woman with cancer developed fever after 7 days of vancomycin therapy followed by rash and, with restarting vancomycin, neutropenia and serum ALT elevations ["up to 3 times normal"], resolving rapidly upon stopping vancomycin).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in pPatients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to vancomycin).

Song SM, Cho MS, Oh SH, Kim KM, Park YS, Kim DY, Lee SG. Liver transplantation in a child with acute liver failure resulting from drug rash with eosinophilia and systemic symptoms syndrome. Korean J Pediatr 2013; 56: 224-6. PubMed PMID: 23741237.

(14 year old girl developed fever, rash and abnormal liver tests 5 weeks after starting vancomycin for a MRSA wound infection [bilirubin 3.3 rising to 15.5 mg/dL, ALT 263 to 1077 U/L, Alk P 440 U/L, eosinophils 3150/µL], worsening despite methylprednisone and undergoing liver transplant within 9 days of onset).

Della-Torre E, Yacoub MR, Pignatti P, Della-Torre F, Sabbadini MG, Colombo G, Tresoldi M. Optimal management of DRESS syndrome in course of infectious endocarditis. Ann Allergy Asthma Immunol 2013; 110: 303-5. PubMed PMID: 23535099.

(75 year old man developed fever and rash 27 days after starting vancomycin, gentamicin and rifampin for endocarditis [bilirubin not given, ALT 264 U/L, Alk P 247 U/L, eosinophils 6%], with resolution within 8 weeks on methylprednisone and IVIG).