ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 605–609
0066-4804/91/040605-05$02.00/0

Vol. 35, No. 4

MINIREVIEW

Antibacterial Activities and Modes of Action of Vancomycin and Related Glycopeptides

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Vancomycin (21) is produced by *Amycolatopsis orientalis* (18) (previously designated *Nocardia orientalis* and *Streptomyces orientalis*). The antibiotic has been marketed for the past 30 years and continues to be marketed, as the hydrochloride salt, to treat deep-seated gram-positive bacterial infections. It is the drug of choice for infections caused by *Staphylococcus aureus*, especially those caused by strains resistant to methicillin. Vancomycin is bactericidal to most gram-positive organisms, but gram-negative organisms are resistant. Vancomycin is not absorbed from the gastrointestinal tract, and the antibiotic is used to treat enterocolitis, especially that caused by *Clostridium difficile*. Vancomycin is in clinical use worldwide. Teicoplanin (4, 33) was recently launched in Italy and France and is under clinical trials in other countries in Europe and in the United States.

STRUCTURE-ACTIVITY RELATIONSHIPS (SAR)

All glycopeptide antibiotics contain a central core heptapeptide. This heptapeptide, I, written in the conventional peptide structure, has a high degree of homology in aromatic amino acids 4 to 7 for this class of antibiotics. In several glycopeptide antibiotics, the remaining amino acids, 1 to 3, are also aromatic, and they belong to the ristocetin class.

Vancomycin-type antibiotics are structurally unique, and amino acids 1 and 3 are aliphatic amino acids with the N-terminal amino acid residue being leucine or its methylated analogs.

A structural representation of glycopeptide antibiotics is shown in Fig. 1.

Several close structural analogs of vancomycin have been reported recently, and these include A51568 factors A and B (14); the M43 group of antibiotics (25); A82846 factors A, B, and C (23); orienticins (35); chloroorienticins (34); eremomycin (6); and MM45289 (11).

Several degradative and chemical interconversions on the above-mentioned antibiotics have been reported over the past 10 years. My coworkers and I (22) have examined the in vitro antimicrobial activities of these compounds against penicillin G-susceptible *S. aureus* X1.1, penicillin G-resistant *S. aureus* V41, methicillin-resistant *S. aureus* X400, methicillin-resistant *S. aureus* S13E, macrolide-resistant *Staphylococcus epidermidis* 270, macrolide-susceptible *S. epidermidis* 222, *Streptococcus pyogenes* C203, *Streptococcus pneumoniae* Park, *Streptococcus* (*Enterococcus*) *faecium* X66, and *Streptococcus* (*Enterococcus*) *faecalis* 2041. A SAR can now be delineated with reference to the antibacterial activity of vancomycin.

Amino acid 1. In the vancomycin-type antibiotics, naturally occurring amino acid 1 is leucine or its methylated analogs (6, 11, 14, 21, 23, 25, 34, 35). The state of methylation of the N-terminal leucine does not greatly affect the antibacterial activity of vancomycin. However, the removal of this crucial amino acid (5, 26), needed for binding of the *N*-acyl-D-alanyl-D-alanine (acyl-D-ala-D-ala) carboxy terminus of UDP-*N*-acetylmuramylpentapeptide to the N-terminal leucine of vancomycin, completely destroys the antibacterial activity of vancomycin (see also Modes of Action section).

The glycopeptide antibiotic synmonicin has been reported to contain *N*-methyl-*p*-hydroxy-phenylalanine (15; see also references 30, 37, and 38), and antibiotic OA7653 has *N*,*N*-dimethylalanine (3, 17) as the N-terminal amino acid in place of the *N*-methylleucine of vancomycin. Both these antibiotics are less active than vancomycin.

Amino acid 2. An analog of vancomycin in which the benzylic hydroxyl group of amino acid 2 is replaced by hydrogen (M43E) has been isolated from a strain of *A. orientalis* (22). This naturally occurring vancomycin analog is half as active as vancomycin.

Catalytic dechlorination of vancomycin (12) occurs initially on the aromatic ring of amino acid 2. Vancomycin is twice as active as this monodechlorovancomycin derivative. On prolonged catalytic dechlorination, the second chlorine on the aromatic ring of amino acid 6 of vancomycin is also removed (12). This didechlorovancomycin is four times less active than vancomycin.

Amino acid 3. A51568B (14) and M43G (22) are the glutamine analogs of A51568A (14) and vancomycin, respectively. These two antibiotics have an additional methylene on amino acid 3. A51568B is fourfold less active than vancomycin, and M43G is half as active as vancomycin. Consequently, the increase in the chain length of asparagine to glutamine reduces the activity of vancomycin.

M43F and M43B are the aspartic acid analogs of vancomycin and M43A, respectively (25). These two antibiotics are at least 10 times less active than vancomycin. CDP-1 (20), the rearranged isoaspartic acid analog of vancomycin, and the corresponding isoaspartic acid analog of M43A (25) are devoid of antibacterial activity.

The negative charge of the aspartate and isoaspartate moieties in M43B, M43F, and the rearranged analogs, along with changed conformational geometry (13) in the rearranged derivatives, seems to hinder the binding of the acyl-D-ala-D-ala carboxy terminus of UDP-*N*-acetylmuramylpentapeptide to vancomycin and contributes to the diminution of biological activity (see also Modes of Action).

Amino acid 4. In several of the vancomycin-type glycopeptide antibiotics, the phenolic group carries a disaccharide unit. In many cases, the first sugar is glucose, and the second sugar is an amino sugar, either L-vancosamine or L-4-epivancosamine. These two sugars can be cleaved selec-

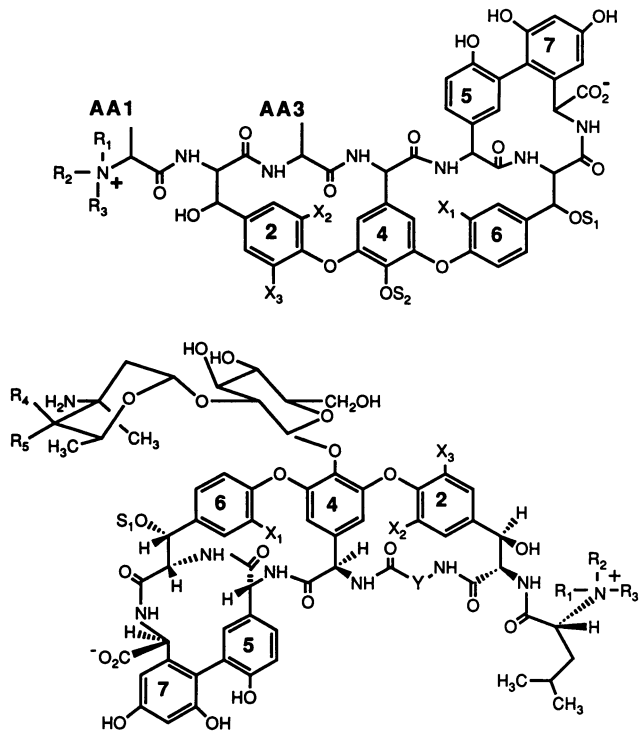

FIG. 1. In the structural representation of these glycopeptide antibiotics (top and bottom), R_1, R_2, and R_3 represent H or CH_3. R_4 and R_5 are H or OH. X_1, X_2, and X_3 are H or Cl. S_1 and S_2 are sugars. Y represents an asparagine, aspartic acid, or isoaspartic acid moiety. Numbers 1 to 7 represent the amino acids of the antibiotic heptapeptide (top), starting at the amino terminal. AA1 and AA3 refer to amino acids 1 and 3, respectively.

tively in a sequential manner (26). The desvancosamine derivatives of vancomycin, A51568A and M43A, and the corresponding aglycones have been obtained (26).

The removal of vancosamine in the above-mentioned three antibiotics reduces activity two- to fivefold. The removal of the second sugar, glucose, restores the in vitro activity, but the in vivo activity is reduced fivefold. The sugars seem to play an important role in imparting enhanced pharmacokinetic properties to this class of antibiotics.

Amino acid 6. Recently, several glycopeptide antibiotics which made possible the delineation of the role of chlorine on biological activity have been isolated. Accordingly, antibiotic A82846B has two chlorines, one on the aromatic ring of amino acid 6 and the other on amino acid 2. A82846A has a chlorine on amino acid 2, orienticin A possesses a chlorine on amino acid 6, and A82846C is devoid of any chlorine substituent. In all other aspects these four antibiotics are identical.

An examination of in vitro antibacterial activity shows that A82846A and A82846B are about 2 to 10 times more active than vancomycin, while orienticin A and A82846C are twofold less active than vancomycin. These data suggest that removal of chlorine in the aromatic ring of amino acid 6 has slight, if any, effect on antibacterial activity. However, removal of chlorine in the aromatic ring of amino acid 2 diminishes the activity 10-fold.

Finally, the selective and sequential removal of first the L-epivancosamine and then the second glucose from amino acid 4 of A82846 was accomplished. These two compounds and A82846B are 2 to 10 times more active than vancomycin. Consequently, it appears that the benzylic amino sugar L-4-epivancosamine of amino acid 6 increases the activity of vancomycin 2- to 10-fold.

Semisynthetic N-acyl and N-alkyl derivatives. Several glycopeptides containing a long-chain aliphatic acyl residue on one of the amino sugars have been reported (8, 9, 19, 32, 39). Some of these compounds were reported to be superior in antibacterial activity and pharmacokinetics to vancomycin (10). Thirty-two N-acyl vancomycins were synthesized and evaluated (27). In the aliphatic N-acyl vancomycins, the mono-N-acyl derivative functionalized on the amino group of the vancosamine sugar is more active than the mono N-acyl vancomycin substituted on the amino acid, *N*-methylleucine. Both types of mono-N-acyl vancomycins are more active than the di-N-acyl vancomycins.

A comparison of the aliphatic mono-N-acyl vancomycins substituted on the amino group of vancosamine reveals that increasing the length of the side chain increases activity. The optimum activity is found when the side chain is a C_9 to C_{11} straight-chain fatty acid residue. When the carbon chain length is greater than 11, the activity drops off. Modification of the side chain with a branched chain or introduction of an amino, bromo, or carbonyl group does not alter the activity.

The SAR of the N-aracyl vancomycins follow a pattern similar to those of the aliphatic N-acyl vancomycins. Accordingly, the mono-N-acyl vancomycins substituted on vancosamine are more active than the mono-N-acyl derivatives functionalized on *N*-methylleucine; and both the above-mentioned mono-N-acyl vancomycins are more active than the corresponding di-N-acyl vancomycins.

A comparison of the aliphatic mono-N-acyl and the aromatic mono-N-aracyl vancomycins substituted on the vancosamine sugar shows that the mono-N-aracyl vancomycins are in general more active than the aliphatic N-acyl derivatives. The most active compounds in the mono-N-aracyl series are the *p*-octylbenzoyl and *p*-octyloxybenzoyl vancomycin derivatives, with a hydrocarbon attached to the aromatic ring.

Finally, a comparison of the antibacterial activities of the parent vancomycin and its N-acyl derivatives shows that, even though in some cases there is slight increase in the in vitro spectrum of the mono-N-acyl derivatives, the in vivo activities do not exhibit any great increase over those of vancomycin.

As an extension to the above-described SAR of N-acyl vancomycins, over 80 N-alkyl vancomycins were synthesized and evaluated (28). A comparison of the antibacterial activities of the N-decyl vancomycins and the corresponding N-decanoyl vancomycins shows that the C_{10} alkyl analogs are more active than the corresponding alkanoyl series. Furthermore, the N-decyl vancomycin is more active in vitro than the parent vancomycin, is equivalent to vancomycin in vivo, and shows a longer elimination half-life in rats.

As in the SAR of the N-acyl vancomycin series, the general trend is that the N-alkyl derivatives substituted on vancosamine are more active than those substituted on *N*-methylleucine and both monosubstituted vancomycins are more active than the corresponding di-N-alkyl vancomycins.

In the aliphatic straight-chain series, increasing the chain length enhanced activity. The optimum seems to be C_{10}. Branching the aliphatic side chains or substituting with oxygen or sulfur did not seem to increase activity. The benzyl derivative and the benzyl derivatives substituted at the 4 position with an aliphatic side chain were more active than the aliphatic series in the in vivo models. The most

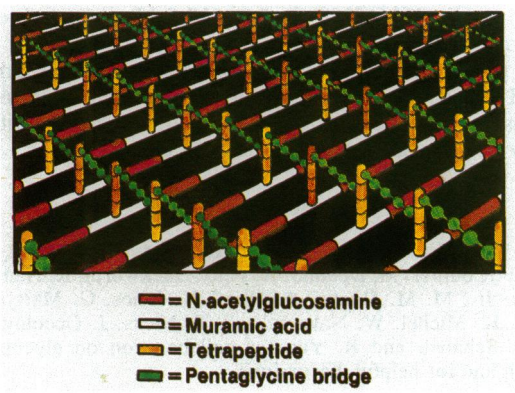

FIG. 2. Schematic representation of a layer of peptidoglycan network in *S. aureus*.

active compounds were the octylbenzyl and octyloxybenzyl derivatives. Substitution at the *para* position of the benzyl moiety with heteroatoms such as oxygen, sulfur, nitrogen, or halogens did not seem to enhance activity. Several compounds in the N-alkyl vancomycin series were more active than vancomycin. The octylbenzyl, octyloxybenzyl, butylbenzyl, butyloxybenzyl, and benzyl derivatives had the best activity and were up to five times more active than vancomycin.

Activities of N-alkyl derivatives against resistant enterococci. Since the recent reported isolation of clinical isolates of *E. faecium* and *E. faecalis* resistant to vancomycin (36), several glycopeptides and their derivatives were tested against 34 susceptible enterococcal strains and 26 resistant enterococcal strains (24, 29). The semisynthetic N-alkyl vancomycin and A82846 derivatives exhibited excellent activity against these resistant enterococci.

Whereas the geometric mean MICs of vancomycin were 1.0 and 263 μg/ml, respectively, against the 34 susceptible enterococci and the 26 resistant enterococci, for the most active N-alkyl vancomycins, the mean MICs were 0.5 to 0.75 μg/ml for the susceptible strains and 4 to 6 μg/ml for the resistant strains (29). For the most active N-alkyl A82846B derivatives, the corresponding values were 0.6 to 0.75 and 2 to 4 μg/ml, respectively (24). Thus, it is clear that not only are the N-alkyl vancomycin and A82846 derivatives five times more active than vancomycin against gram-positive bacteria, but more importantly, the semisynthetic N-alkyl derivatives are active against vancomycin-resistant *Enterococcus* strains at clinically relevant MICs.

MODES OF ACTION

The cell walls of gram-positive bacteria appear uniform under the electron microscope and are made up of peptidoglycan, protein, and teichoic acids.

In the peptidoglycan of *S. aureus* (Fig. 2), the long horizontal chains are made up of *N*-acetylglucosamine and muramic acid. Tetrapeptides are attached to the muramic acid units. Finally, the interpeptide pentaglycine bonds complete the rigid peptidoglycan framework.

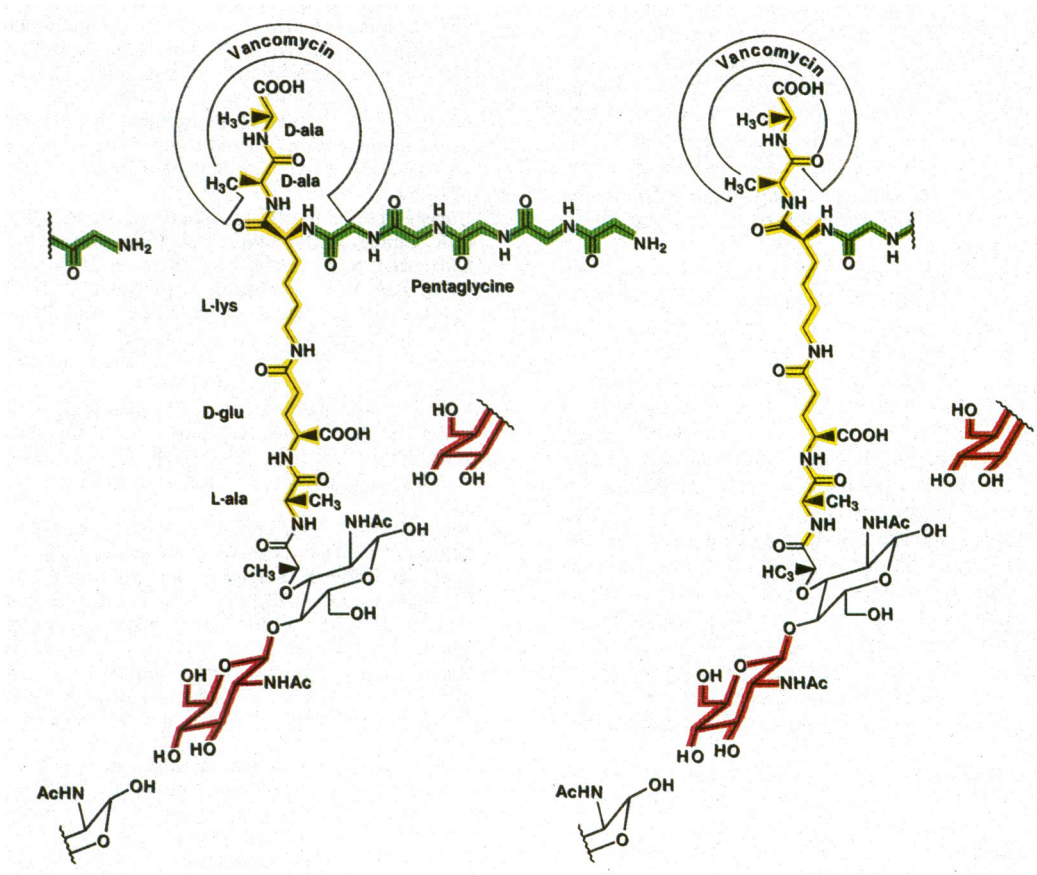

FIG. 3. Chemical representation of the mode of action of vancomycin.

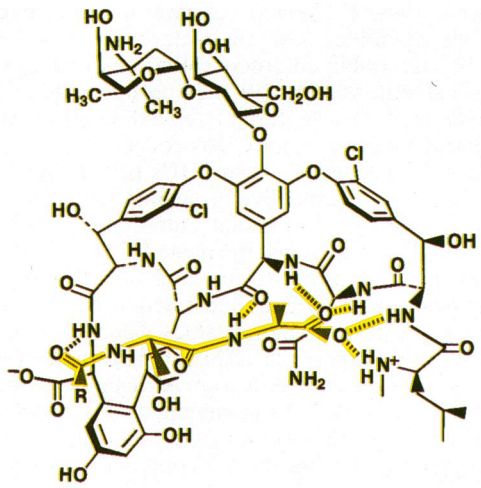

FIG. 4. Cell wall acyl-D-ala-D-ala terminus binding to vancomycin.

Biochemical studies suggest that the modes of action of vancomycin and other glycopeptides involve the inhibition of peptidoglycan synthesis. Vancomycin forms a stoichiometric 1:1 complex with the peptidoglycan precursor UDP-*N*-acetylmuramylpentapeptide (7) by forming hydrogen bonds (Fig. 3).

The transglycosylase enzyme that transfers the disaccharide of the peptidoglycan precursor to the growing glycan polymer of the cell wall peptidoglycan is inhibited (1, 2), presumably due to the steric bulkiness of the glycopeptide-peptidoglycan precursor (31). Furthermore, even if some glycan chain synthesis occurred, since the acyl-D-ala-D-ala portion of the peptidoglycan precursor is enveloped by the larger glycopeptide, the transpeptidase enzyme reaction is probably inhibited (31). It seems that both the transglycosylase and transpeptidase enzyme reactions that complete the synthesis of the rigid cell wall peptidoglycan may be inhibited by the glycopeptides.

Computer and molecular modeling (16, 40) show how the acyl-D-ala-D-ala carboxy terminus of the cell wall subunit is held firmly by several hydrogen bonds to the N terminus of the glycopeptide antibiotic (Fig. 4).

This SAR analysis of vancomycin-type glycopeptides is entirely consistent with the mode of action of this class of antibiotics. There are two chemical modifications in the close vicinity of the binding site of the vancomycin molecule that markedly affect the antibacterial activity of the antibiotic. Accordingly, the removal of the crucial N-terminal leucine of vancomycin completely destroys the antibacterial activity of the antibiotic. The introduction of a new carboxylate moiety, by substituting the carboxamido unit of asparagine of vancomycin to aspartic acid in M43F, reduces the antibacterial activity substantially. Thus, any structural changes near the vancomycin N terminus that hinder binding to the acyl-D-ala-D-ala carboxy terminus of UDP-*N*-acetylmuramylpentapeptide diminish the antibacterial activity of vancomycin.

Other chemical modifications of vancomycin farther removed from the binding site do not alter the antibacterial activity greatly and in some instances may provide derivatives with greater antibacterial activity or better pharmacokinetic properties.

It should be pointed out, however, that although A82846A (eremomycin; MM45289) is 5- to 10-fold more active than vancomycin against gram-positive bacteria, its affinity to the model peptidoglycan diacetyl-L-lysyl-D-alanine-D-alanine is 23-fold lower (11). Further studies are needed, therefore, to establish a correlation between the antibacterial activity and affinity of cell wall model peptides to glycopeptides.

ACKNOWLEDGMENTS

I am pleased to acknowledge my colleagues N. E. Allen, D. R. Berry, F. Counter, M. Debono, A. Felty-Duckworth, R. Hamill, H. Higgins, Jr., M. M. Hoehn, A. Hunt, N. Jones, G. Marconi, K. Merkel, K. Michel, W. Nakatsukasa, T. Nicas, J. Occolowitz, J. Ott, A. Schabel, and R. Yao for collaboration on glycopeptide research and for helpful discussions.

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