A Review of Teicoplanin Used in the Prevention and Treatment of Serious Infections Caused by Gram-Positive Bacteria and Compared Its Effects with Some other Antibiotics

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ABSTRACT

Teicoplanin is an antibiotic used in the prevention and treatment of serious infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis*. It is a semi-synthetic glycopeptide antibiotic with a spectrum of activities similar to vancomycin. Its mechanism of action is inhibition of bacterial cell wall synthesis teicoplanin is marketed by Sanofi Aventis Cooperation under the brand name of Targocid. It has been shown that oral administration of teicoplanin is effective in the treatment of *Pseudomembranous colitis* and *Clostridium difficile*-associated diarrhoea, with comparable efficacy to vancomycin. The effectiveness of this antibiotic is associated with its carbon chain length. It's tried in this review article to introduce teicoplanin synthases, structure and its structure effect on treatment and also introduce the advantages of teicoplanin in bacterial infection treatment and compared its effects with some other antibiotics like vancomycin and linezolid. Based on the above data, it can be concluded that teicoplanin usage, specially intervenes injection of it, is a successful antibiotic treatment against bacterial infections caused by Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). The teicoplanin effect is directly related to the length of its carbon chain. It was shown that treatment with combination of teicoplanin and vancomycin or teicoplanin and linezolid have more influence over the treatment process. The most important advantage of teicoplanin usage in treatments is its lower side effects on patients than other antibiotics.

Key word: Carbon chain, Gram-positive, Methicillin-resistant *Staphylococcus aureus* (MRSA), Teicoplanin.

INTRODUCTION

Chemical Structure

In fact, teicoplanin is composed of several chemicals, 5largeparts calledteicoplanin A2-1 through A2-5 and 4 small parts called teicoplanin R5-1 through R5-4 and has aglycopeptide core called teicoplanin A3-1. This ring binds to mannose and N-acetyl glucosamine. The major and minor components also contain a third carbohydrate moiety-β-D-glucosamine and differ only by the length and conformation of a side chain attached to it. The overall structure of this compound can be seen in Figure 1.

Teicoplanin biosynthesis

Teicoplanin refers to a set of natural products isolated from the fermentation broth of a strain of *Actinoplanes teichomyceticus*, consisting of five subcategories. These subcategories
possess a common aglycone, or core, composed of seven amino acids bound by peptide and ether bonds to form a four-ring system and differ by the fatty acyl side-chain attached to the sugar. The origin of these seven amino acids in teicoplanin biosynthesis was studied by $^1$H and $^{13}$C nuclear magnetic resonance. The results show that amino acids AA1, AA2, AA4, AA5, and AA6 are derived from tyrosine, and amino acids AA3 and AA7 are derived from acetate. Specifically, teicoplanin contains 4-hydroxyphenylglycine and 3, 5-dihydroxyphenylglycine residues, a chlorine atom attached on each of the tyrosine residues, and three sugar moieties, including N-fatty acyl-β-D-glucosamine, N-acetyl-β-D-glucosamine, and D-mannose.

Gene cluster

The investigation of teicoplanin biosynthesis gene cluster shows ORF 49 in the path of biosynthesis, transfer, resistance, and regulation of gene expression. ORF 35 identified in this path is similar to gene clusters relevant to other glycopeptide genes. The function of each of these genes is described by Li and co-workers.

Heptapeptide backbone synthesis

Analysis indicated tyrosine and three types of non-proteinogenic amino acids, (S)-4-hydroxyphenylglycine, 3, 5-dihydroxyphenylglycine, and β-hydroxytyrosine as the glycopeptide building blocks of teicoplanin. In total, six of the seven total amino acids composing teicoplanin backbone are composed of non-proteinogenic or modified amino acids. Cooperation and activity of eleven enzymes are responsible for preparation and synthesis of these six residues. Teicoplanin contains two chlorinated positions, 2 (3-Cl-Tyr) and 6 (3-Cl-β-Hty). Halogenase ORF 8 has been proposed to have a role in catalyzing the halogenation process of these amino acids. It seems that chlorination process occurs at early stages in Teicoplanin biosynthesis and prior to phenolic oxidative coupling, with the possibility of tyrosine or β-hydroxytyrosine being the substrate of chlorination. The biosynthesis of heptapeptide root is performed by four nonribosomal peptide synthetases called TeiA, TeiB, TeiC, and TeiD. Each module has a domain for amino acid selection and activation through aminoacyl-AMP. The catalytic domain in modules 3 and 4 of non-ribosomal peptide synthetase are linearly and activated by (S)-4-hydroxyphenylglycine and 3, 5-dihydroxyphenylglycine. In addition to these modules for amino acid selection and activation, each module has a thiolation domain modified with phosphopantetheine to provide a thiol for covalent aminoacyl-S-enzyme formation.

Modification after heptapeptide backbone formation

Once the heptapeptide backbone has been formed and synthesized, the process of catalyzing the linear structure is begun. Studies on gene disruption indicate that cytochrome P450 oxygenase is an enzyme performing the coupling reactions. OxyB has been suggested to form the first ring with coupling residues 4 and 6. Then, OxyA couples residues 2 and 4, followed by the formation of a C-C bond between residues 5 and 7 by OxyC. Fourth enzyme catalyzes the coupling of residues 1 and 3 that for this purpose, OxyB/OxyA/OxyC play a role. The process of specific glycosylation occurs after the formation of the heptapeptide aglycone. Given to the data collected for glycosylation of the teicoplanin aglycone it is shown that three separate glycosyltransferases are required. Two of these glycosyltransferases are involved in the addition of the N-fatty acyl-β-D-glucosamine and N-acetyl-β-D-glucosamine units. The third enzyme, which is a mannosyltransferase, is responsible for the addition of the D-mannose unit onto residue 7. The fatty acyl chain is connected by amide bond to the glucosamine moiety by the action of an acyl transferase. In addition to glycosylation, some genes have been suggested to code for deacylases.

Summary of antibacterial activity of teicoplanin

Previous studies have indicated high inhibitory activity of Teicoplanin against Staphylococcus aureus, as well as those resistant to methicillin and oxacillin. The general similarity of teicoplanin and vancomycin is also shown. All S. aureus strains are sensitive to teicoplanin, although the relative susceptibility of coagulase-negative staphylococci to teicoplanin and vancomycin varied. Studies have shown that Clostridium species such
as *C. diffilce*, *C. perfringens*, *Peptostreptococcus* species, *Propionibacterium acens*, *Corynebacterium jeikeium* and resistant species of *Corynebacterium* group D2 are sensitive to low concentrations of teicoplanin\(^{28, 29}\).

The minimum bactericidal concentration (MBC) of teicoplanin is usually less than or equal to 2 dilutions higher than the minimum inhibitory concentration (MIC\(_{90}\)) for *Streptococcus pneumoniae*, *S. aureus*, *S. epidermidis* and in some studies for some samples of coagulase-negative staphylococci\(^{25, 30}\). The in vitro bactericidal action for the teicoplanin, similar to vancomycin, is slow. Teicoplanin in combination with aminoglycosides shows synergistic inhibitory activity against most bacteria of *S. aureus*, coagulase negative *staphylococci* and *enterococci*. Susceptibility of *E. faecium* to various antibiotics has been shown a significant increase in resistance to penicillin G and gentamicin, but susceptibility to teicoplanin and vancomycin is stable. In animal models of Gram-positive endocarditis, teicoplanin and vancomycin similarly, reduction of bacterial titers in cardiac valvular vegetations was examined a few hours after drug administration, but 10 days after treatment, higher percentage of vegetation by teicoplanin was free of contamination\(^{31-33}\).

**Introducing the pharmacokinetic properties of teicoplanin**

Result of injecting 6 mg/kg teicoplanin in the mean peak serum concentration at 30 minutes and 4 hours after intravenous and intramuscular injection has been reported 43 and 12 mg/l, respectively. Instead state, the concentration of intravenous teicoplanin after intravenously injecting 6 and 12 mg/kg after 12 hours has been reported 14 and 23 mg/l, respectively. And the same results were obtained after 24 hours. Teicoplanin absorption rate after intramuscular administration is equivalent to the rate after intravenous injection. It seems that injecting a dose of 15 mg/kg is needed after a dose of 8mg/kg in day there after to maintain the concentration above 10 mg/l of teicoplanin in neonates\(^{34}\).

Apparent volume of distribution at steady state after intravenous injection of 6 to 15mg/kg teicoplanin was approximately 0.8 to 1.6kg/l that was higher than reports in previous studies in which serum samples were collected for a short period. The average concentration of teicoplanin in atrial appendage was 8 / 2-7 / 3 times the average concentration simultaneously obtained in serum, and the highest concentrations in the heart and pericardium tissue was 4 hours after an intravenous dose of 800 mg. Penetration into the cerebrospinal fluid is minimal after intravenous administration, but drug concentrations in the cerebrospinal fluid is reported more than 40 milligrams per liter after intravenous administration of teicoplanin at a dose of 20 mg per 24 or 48 hours\(^{35, 36}\).

Body metabolism rate for teicoplanin is slight (about 3%). Total body clear ance of teicoplanin after intravenous administration of 3 to 30 mg/kg in healthy volunteers is in the range 10-13ml/h/kg. Renal clearance is 8 to 12ml/h/kg which implies that it is almost eliminated by renal mechanisms are. On average, studies in which the duration of sample collection is 3 weeks after the last dose have shown that elimination half-life of teicoplanin will be 155-168 h after intravenous administration and 182 hours after the intramuscular injection.

Total body and renal clearance rates for teicoplanin correlates with creatinine clearance and reduced in patients with impaired renal function. Teicoplanin cannot be removed by hemodialysis cycle, regardless of the dialysis membrane\(^{37, 38}\).

In patients with a history of intravenous drug use treated with teicoplanin for bacterial endocarditis, the average amount of total body and renal clearance is reported higher and more diversified than that in healthy subjects and elimination half-life is reduced\(^{39, 40}\).

**An example of teicoplanin treatment effects**

Studies relevant to the teicoplanin effects in treating bacteraemia and intravascular infections in patients without neutropenia stay largely non-comparative. Comparative investigations have shown that daily administration of 6 mg/kg teicoplanin has the same effect with 12-hour administration of 15 mg/kg vancomycin. Daily use of only 400-800 mg teicoplanin cures 84 to 93% of patients with bacteraemia caused mostly
by *S. aureus* clinically and bacteriologically and is successful in 90 to 100% of patients with streptococcal or enterococcal endocarditis. Recovery is obtained in 89 to 100% of patients with skin and soft-tissue infections (caused mainly by *S. aureus* or *S. epidermidis*) treated with 200 to 800 mg teicoplanin once a day intravenously or intramuscularly.

Non-comparative tests of teicoplanin (usually 6 mg/kg once daily) in patients with acute/chronic osteomyelitis or septic arthritis caused by gram-positive bacteria, have led to clinical cure in 83 to 100% of patients.

A combination of teicoplanin and ciprofloxacin is significantly more effective than either ciprofloxacin or ceftriaxone alone in relieving respiratory tract infections. In non-comparative studies, teicoplanin alone results in clinical cure or improvement in approximately 91% of patients with respiratory tract infections. In the treatment of *Clostridium difficile* resulting in severe diarrhea and colitis, oral administration of 100 mg teicoplanin twice a day and 500 mg vancomycin four times a day can improve 96% and 100% of patients, respectively.

Once teicoplanin is used as the initial treatment in patients with cancer and neutropenia, its effect is similar to that of vancomycin. Teicoplanin was associated with a more tolerant with a lower incidence of super infection caused by *Candida* species, indicating that teicoplanin is a viable alternative to vancomycin. Adding teicoplanin to piperacillin plus amikacin has no clinical effectiveness. Controversy still remains over the need for these drugs, from drug selection and timing for the introduction of antibiotics to experimental diets that all depends on environmental conditions.

While no improvement was observed in patients, they were prescribed with teicoplanin, and positive results were shown in patients with Gram-positive bacterial infection. Teicoplanin was effective for secondary treatment of patients who had a negative response to experimental treatment with either ceftazidime alone or in combination with amikacin, piperacillin plus amikacin, or one of the cephalosporin and aminoglycoside antibiotics.

In patients undergoing hip and knee arthroplasty, only intravenous dose of 400 mg teicoplanin has a similar effectiveness with 4 post-surgery doses of cefamandole or 5 post-surgery doses of cefazolin in anesthesia induction. Clinical experience with teicoplanin limited in infants and children. However, preliminary data in children with sepsis, upper and lower respiratory tract infection, skin or soft tissue infection and in febrile children with neutropenia shows that 6 to 10 mg/kg teicoplanin once a day is effective in the treatment of Gram-positive infections.

As a result of the efficiency often teicoplanin against Gram-positive infections, once-daily intravenous or intramuscular injection of teicoplanin is suitable for outpatients. After the success often teicoplanin in out patients or patients...
at first hospitalization and thereafter, it showed
success in cares after discharge. Teicoplanin has
been successfully used to treat skin and soft tissue
infection, bone and joint infection, and media stitits
after coronary artery bypass surgery.57

Comparing the effect of teicoplanin and linezolid

Linezolid is the only commercially available oxazolidinone using for Gram-positive infections, although, a few papers are published particularly on its use in acute illnesses.58, 59. Therefore, a prospective randomized study was conducted to compare linezolid with glycopeptide antibiotic, teicoplanin, for suspicious or proven treatment of gram-positive infections in intensive care unit population by Cepeda et al.58.

In this regard, a prospective double-blind
double-dummy study was designed. The patients
were randomly divided into two groups: A) patients
who received intravenous linezolid (600 mg / 12hours) plus intravenous placebo-teicoplanin
(one dose per 48 hours and after three
injections, one dose per 24 hours). B) Patients
who received teicoplanin (3 injections per 12 hours at a
dose of 800 mg and then one injection per 12
hours) plus placebo-linezolid (one dose per 48
hours and after three injections, one dose per 24
hours). Other antibiotics were used in combination
with testing drugs in experimental treatment. Clinical
and microbiological evaluation of the first week was
done daily and then, in day 8 and 21.

In this study, 100 patients received
linezolid plus placebo-teicoplanin and 102 patients
received teicoplanin plus placebo-linezolid. Figures
obtained from population were similar in both
groups. At the end of treatment, clinical success [71
(78.9%) linezolid versus 67 (72.8%) teicoplanin]
and microbiological success [49 (70.0%) versus 45
(66.2%)] were similar. Side effects and the success
rate of short-term and long-term follow-up were also
the same. Linezolid was superior in the initial
distance against the colonization of methicillin-resistant
Staphylococcus aureus (MRSA)60, 61. There is an
uncertainty about the effects of teicoplanin
compared with vancomycin in their effectiveness
on renal function. Some previous studies have
shown that teicoplanin is less nephrotoxic than
vancomycin. To evaluate the efficacy and safety of
vancomycin in comparison with teicoplanin in
patients with proven or suspected infection, Cavalcanti et al., searched articles published in
different languages in association with comparing
the efficacy of teicoplanin and vancomycin. They
evaluated independently methodological quality
and data extracted using a standardized data
extraction form in various articles. They gathered
information from 24 independent studies and
concluded that teicoplanin reduces the risk of
nephrotoxicity compared with vancomycin (risk ratio
0.66, 95% confidence interval 0.48 to 90). They
reported the effect of teicoplanin and vancomycin
the same for clinical improvement (RR 1.03, 95%
CI 0.98 to 1.08), microbiological cure (RR 0.98, 95%
CI 0.93 to 1.03) and mortality (RR 1.02, 95% CI
0.79 to 1.30). Side effects including skin rash (RR
0.57, 95% CI 0.35 to 0.92), red man syndrome (RR
0.21, 95% CI 0.08 to 0.59) and total side effects (RR
0.73, 95% CI 0.53 to 1.00) resulted from
administering teicoplanin compared to vancomycin
were observed less. The risk of nephrotoxicity with
teinoplanin patients with (RR 0.51, 95% CI 0.30
to 0.88) or without (RR 0.31, 95% CI 0.07 to 1.50)
aminoglycosides has been less.

Finally and generally, these studies
showed that, teicoplanin and vancomycin are
effective in treating patients with proven or
suspected infection. Yet, incidence of adverse
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administration will be lower. Since the group was
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requiring dialysis, it did not become clear that

Comparing the effect of teicoplanin and vancomycin

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effects, including nephrotoxicity with teicoplanin
administration will be lower. Since the group was
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requiring dialysis, it did not become clear that
different effects on kidney function should be under the impression of what antibiotics prescribed. Although it seems logical that teicoplanin to be prescribed for patients with a high risk of AKI requiring dialysis due to the lower risk of nephrotoxicity resulted from antibiotic usage\textsuperscript{31}. Based on the above data, it can be concluded that teicoplanin usage, specially intervenes injection of it, is a successful antibiotic treatment against bacterial infections caused by Gram-positive bacteria, particularly methicillin-resistant \textit{Staphylococcus aurous} (MRSA). The teicoplanin effect is directly related to the length of its carbon chain. It was shown that treatment with combination of teicoplanin and vancomycin or teicoplanin and linezolid have more influence over the treatment process. The most important advantage of teicoplanin usage in treatments is its lower side effects on patients than other antibiotics.

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