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Clinical Pharmacology of Teicoplanin in Neonates: Effects and Pharmacokinetics

*Gian Maria Pacifici[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Teicoplanin is a glycoside antibiotic which consists of five closely related glycopeptide antibiotics with similar antibacterial properties to vancomycin that were first isolated in 1976. Teicoplanin is active against many gram-positive anaerobe microorganisms and is particularly potent against clostridium species. It is also active against most Listeria, enterococci and staphylococci including methicillin-resistant strains. Nonviridans and viridans streptococci, Streptococcus pneumoniae, and enterococci are inhibited by teicoplanin. Teicoplanin has been used to treat a wide variety of infections, including osteomyelitis and endocarditis caused by methicillin-resistant and methicillin-susceptible staphylococci, streptococci, and enterococci.

Teicoplanin has a spectrum of antimicrobial action similar to vancomycin, but teicoplanin has some advantages in that it only needs to be given once a day, does not need to be given as slowly as vancomycin and can be given by intramuscular injection. Teicoplanin cannot be given by mouth. Teicoplanin is excreted unchanged in the urine. The half-life of teicoplanin is 100 hours in adults and $2^{1/2}$ days in children. Teicoplanin has a large distribution volume and long half-life and a loading dose is recommended. In infants, the loading dose of teicoplanin is 16 mg/kg administered intravenously followed by 8 mg/kg once daily. The target trough concentration of teicoplanin ranges from 15 to 30 µg/ml. The incidence of hepatic dysfunction, renal impairment and thrombocytopenia is 14.8%, 20%, and 14%, respectively, when the serum teicoplanin concentrations range from < 20 µg/ml and ≥ 20 µg/ml. The aim of this study is to review the effects and the pharmacokinetics of teicoplanin in neonates.

Key Words: Effects, Neonate, Pharmacokinetics, Teicoplanin.

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Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

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1-INTRODUCTION

Teicoplanin, a glycoside antibiotic, is a useful antimicrobial agent with similar spectrum of antimicrobial activity to vancomycin, but has some advantages in that it only needs to be given once a day, does not need to be given as slowly as vancomicin and can be given by intramuscular injection. Vancomicin-resistance organisms are sometimes sensitive to teicoplanin. Teicoplanin is a complex of five closely related glycopeptide antibiotics with similar antibacterial properties to vancomycin that were first isolated in 1976. Teicoplanin is active against many gram-positive anaerobes and is particularly potent against clostridium species. It is also active against most Listeria, enterococci and staphylococci (including methicillin-resistant strains). Teicoplanin cannot be given by mouth and this drug is excreted unchanged in the urine (1).

Teicoplanin inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-Alanyl-D-alanine terminus of cell wall precursor units. Because of the large molecular size, glycopeptides are unable to penetrate the outer membranes of gram-negative bacteria. Glycopeptides are generally bactericidal against susceptible strains, except for enterococci. Teicoplanin is active against methicillin-susceptible and methicillin-resistant staphylococci, which typically have Multiple Indicator Cluster Surveys (MICS) of <4 µg/ml. The MICS for Listeria monocytogenes, Corynebacterium species, and anaerobic gram-positive cocci range from 0.25-2 µg/ml. Nonviridans and viridans streptococci, Streptococcus pneumoniae, and enterococci are inhibited by concentrations ranging from 0.01-1 µg/ml. Teicoplanin is highly bound by plasma proteins (90-95%), and in vitro studies show that protein binding affects its antibacterial activity. In adults, teicoplanin has an extremely long serum elimination half-life, up to 100 hours in patients with normal renal function (2). In children, the half-life is about $2^{1/2}$ days. Teicoplanin has a high distribution volume making an initial loading dose advisable. This drug penetrates most tissue fluid well, but penetration into the cerebral spinal fluid is unsatisfactory and often unpredictable (1).

Teicoplanin has been used to treat a wide variety of infections, including bone and join infections, osteomyelitis and endocarditis, caused by methicillin-resistance and methicillin-susceptible staphylococci, streptococci, and enterococci (2).

Gram-positive bacteria, notably coagulase-negatively staphylococci, have become an important cause of infection in neonates (3). Furthermore, many of these pathogens are now resistant to multiple antibacterial agents (4). A combination of ampicillin plus aminoglycoside is recommended as first-line treatment for early-onset sepsis. For late-onset sepsis acquired in neonatal intensive care units anti staphylococcal agents such as glycopeptides should be substituted for ampicillin, particularly if methicillin-resistant staphylococci are frequently isolated in the neonatal unit. Although, vancomycin is effective in this setting, it is associated with a high incidence of anaphylactic reactions (5) and with auditory and renal toxicity (5, 6).

Teicoplanin is active against gram-positive bacteria, and has a good general and renal safety profile (6) confirmed in both term and preterm newborns (7). Strains of enterococci once were once uniformly susceptible to glycopeptides. Glycopeptide-resistant strains of Enterococcus faecium, have emerged as major nosocomial pathogens in the United States of America. Enterococcal resistance to glycopeptides is the result of alteration of the D-Alanyl-D-alanine target to D-Alanyl-D-lactate or D-Alanyl-D-serine, which bind glycopeptides poorly, due to

the lack of a critical site for hydrogen bonding (8).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; July 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Teicoplanin" keyword AND "Neonetes" keyword AND "Pharmacokinetics teicoplanin neonate" keyword AND "Pharmacokinetics teicoplanin neonate" keyword AND "Infants" keyword), were used to search for the relevant literature. In addition, the book Neonatal Formulary (1) was consulted.

3-RESULTS

3-1. Treatment

3-1-1.Treatment of infants < 1 month old

Give a 16 mg/kg loading dose by intravenous injection followed by 8 mg/kg given by intravenous or intramuscular injection once every 24 hours. Treat proven septicemia for at least 7 days. Double the dosage interval in renal failure (1).

3-1-2.Treatment of older infants

Give three 10 mg/kg intravenous doses 12 hours apart. Then give 10 mg/kg once every 24 hours (1).

3-2. Evaluation of teicoplanin concentrations and safety in neonates

Infection with methicillin-resistant Staphylococcus aureus significantly increases morbidity and mortality in neonatal intensive care units. Thus, prompt treatment with appropriate antimicrobial agents using adequate dosage is required (9). Teicoplanin, a glycopeptide antibiotic, has been used to treat methicillin-resistant Staphylococcus aureus infections. Since teicoplanin has a long elimination half-life and a large distribution volume an initial loading dose is required to rapidly achieve the optimal exposure. It is commonly considered that the trough concentration of teicoplanin be ≥10 μg/ml for methicillin-resistant Staphylococcus aureus infections and ≥20 μg/ml for deep-seated infections such as endocarditis, bone and join infections, and osteomyelitis (10, 11).

Recently, it has been reported that it is necessary to achieve a trough concentration of ≥15 μg/ml to obtain the high efficacy of teicoplanin for methicillin-resistant Staphylococcus aureus infections, and 15-30 μg/ml has been recommended as the new target trough range (12). However, there are limited data regarding dosage and subsequent trough concentrations of teicoplanin in neonates (7), and there are no data on whether the recommended loading and maintenance doses for neonates reach the target trough range (15-30 μg/ml) as a surrogate marker for the anti-methicillin-resistant Staphylococcus aureus efficacy of teicoplanin. It has been shown that nephrotoxicity and hepatotoxicity were caused at a teicoplanin concentrations >60 μg/ml, and thrombocytopenia was found at a trough concentration of >40 μg/ml in adult patients treated with teicoplanin (13).

Thus, the safety of teicoplanin at a trough concentration ≥20 μg/ml has been confirmed in adult patients (14). However, there are few reports regarding the adverse reactions in neonates treated with teicoplanin (7). **Table.1** shows the median teicoplanin trough concentrations and the number of neonates achieving a trough concentration of ≥ 7.0 μg/ml on day 3 or 4

divided into each loading dose regimen. To examine the factors that affect the fluctuation of teicoplanin serum concentrations, correlation analysis were performed. There were significant correlations between cumulative doses at day 3 or 4 and trough concentration ($r = 0.724$; $P<0.001$). There were no significant correlations between serum creatinine and concentration/dose ratio, body weight and concentration/dose ratio, corrected gestational age and concentration/dose ratio, and postnatal age and concentration/dose ratio.

Table.2 shows the incidence of adverse reactions in neonates treated with teicoplanin at a concentration of < 20 μg/ml or ≥ 20 μg/ml. The incidence of hepatic dysfunction, renal impairment and thrombocytopenia was 14.8%, 20%, and 14%, respectively. There was no significant difference in the incidence of adverse reactions between the trough concentration < 20 μg/ml and ≥ 20 μg/ml groups. The incidence of grade 3 hepatic dysfunction, renal impairment and thrombocytopenia was 7.4%, 4%, and 11.1%, respectively. There was no significant difference in the incidence of adverse reactions between the trough concentration < 20 μg/ml and ≥ 20 μg/ml groups (15).

The results of the analysis of the loading dose and subsequent concentration showed that the median trough concentration in the loading dose regimen of > 12-16 mg/kg on day 1, followed by > 6-8 mg/kg every 12 hours was 8 μg/ml. Moreover, the percentage achieving a trough concentration of ≥ 15 μg/ml in neonates who received > 12 mg/kg on day 1, followed by > 6 mg/kg every 24 hours was 70%. These results indicate that recommended teicoplanin dosage is appropriate for achieving the new target trough range of 15-30 μg/ml (12). It is well known that changes in the development of renal function in neonates are correlate not with postnatal age but with corrected gestational age (16). Moreover, Kimura et al. (17) indicated that corrected gestational age, serum creatinine and body weight were important factors that correlate with individual estimates of vancomycin clearance in neonates. Considering these findings, the present results suggest that teicoplanin trough concentration after administrating the loading dose increases in premature infants and depends both on body weight and renal function. In the maintenance dose regimen > 6-8 mg/kg every 24 hours, the median trough concentration was 18.5 μg/ml. Moreover, the percentage of a trough concentration ≥ 15 μg/ml in neonates who received >6-8 mg/kg every 24 hours was 83.3%, suggesting that the recommended dosage is an appropriate dosage to maintain a trough concentration of 15-30 μg/ml in neonates with normal renal function.

Contrary to the loading dose analysis, body weight, renal function and corrected gestational age were not related to fluctuation factors of teicoplanin trough concentration in neonates with normal renal function. Therefore, other factors or multiple factors including age, body weight and renal function might be involved in fluctuation factors of teicoplanin trough concentration at the maintenance dose administration. Yamada et al. (15) revealed that the recommended teicoplanin dosage for neonates achieves and maintains trough concentration of 15-30 μg/ml and that teicoplanin trough concentration in neonates depends both on body weight and renal function at the loading dose. The incidence of adverse reactions is independent of high trough concentration (≥ 20 μg/ml) and thus it might be possible to set the target trough concentration at ≥ 20 μg/ml for deep-seated infections such as endocarditis, bone and joint infections, and osteomyelitis in neonates.

3-3. Treatment with teicoplanin against staphylococcal infection in neonates

Septicemia remains an important problem in neonatal intensive care associated with high rates of morbidity and mortality (18, 19). Currently, Staphylococcus aureus and coagulase-negative staphylococci represent the most frequent isolated nosocomial pathogens from neonates in neonatal intensive care units (7, 20). These microorganisms show significant resistance to methicillin and/or aminoglycosides, which may be as high as 70-90%, thus glycopeptide antibiotics are used in many neonatal intensive care units (4, 19-21).

Vancomicin is a glycoside antibiotic that has been used in the neonatal intensive care units for many years, despite its side-effects. Teicoplanin, another glycopeptide antibiotic, which has similar clinical efficacy, but fewer side-effects compared with vancomycin, has become the preferred antibiotic (7, 22). The literature on the clinic effect of teicoplanin is scarce (7, 20, 23). Yalaz et al. (24) evaluated the clinical and bacteriological efficacy and potential side-effects of teicoplanin in neonates with proven staphylococcal infection. A total of 909 neonates were admitted to the neonatal intensive care unit (24). The gestational age of 695 (76.5%) neonates was < 37 weeks and 663 neonates (73.0%) had a birth weight < 2,500 grams. The demographic characteristics of the neonates admitted to neonatal intensive care units who had staphylococcus septicemia are summarized in **Table.3**. There were 83 proven episodes of septicemia in 75 neonates. Staphylococcus septicemia was the most frequent cause of neonatal sepsis (n=37, 44.6%). Of these, 26 (70.2%) were caused by coagulase-negative staphylococci, and 11 (29.7%) by staphylococcus aureus. Neonates with Staphylococcus aureus sepsis had significantly lower gestational age ($P<0.05$) and birth weight ($P<0.05$) compared with neonates with coagulase-negative staphylococci sepsis. The mean duration of teicoplanin therapy was 11.6 $\pm$ 2.3 days. The rate of bacteriological care was 89.2% for all patients and 100% for the survivors, and was achieved at 4.8 $\pm$ 1.6 days. There were no significant differences between the infants with coagulase-negative and Staphylococcus aureus sepsis for risk factors and outcomes of teicoplanin in neonates with septicemia (**Table.4**). As shown in **Table.4**, a significantly greater proportion of the former group required mechanical ventilation for at least 3 days ($P<0.01$), although their time to diagnosis was significantly shorter compared to neonates with coagulase-negative staphylococcus infection ($P<0.01$). The most important risk factors for staphylococcal septicemia in both groups were: at least 3 days of total parenteral nutrition (94.5%); central venous catheterization (59.5%); and at least 3 days of mechanical ventilation (59.5%). On comparing the two groups (Staphylococcus aureus and coagulate-negative sepsis), the difference between the proportion of neonates who had required teicoplanin for at least 3 days was not significantly different, but significantly more neonates in the coagulase-negative staphylococci had central venous catheterization ($P<0.01$; **Table. 4**) These authors assessed various clinical and laboratory parameters of the infants with proven septic episodes caused by coagulase-negative staphylococci aureus, who were treated with teicoplanin (**Tables 5 and 6**).

Based on the results of previous study (25), an initial empirical antibiotic therapy protocol was started as follows: in early-onset sepsis - combination of sultamicilin and an aminoglycoside; and in late-onset sepsis - combination of a glycopeptide and a carbapenem (and/or antifungal therapy). A loading intravenous dose of 16 mg/kg of teicoplanin was given on the first day,

followed by 8 mg/kg daily. Antibiotic therapy was discontinued 72 hours after a negative blood culture was obtained. There were no significant differences between the patients with coagulase-negative and Staphylococcus aureus sepsis for these parameters. The antibiotic susceptibility of the microorganisms were as follows: coagulase-negative - teicoplanin and vancomycin 100%, gentamicin 50%. Staphylococcus aureus - teicoplanin and vancomycin 100%, clindamycin and gentamicin 54.5%. Methicillin resistance of coagulase-negative was 92.3% and Staphylococcus aureus was 72.7%. None in either group had side-effects. There have been many reports of the considerable resistance of coagulase-negative and Staphylococcus aureus to methicillin in neonatal intensive care units. The glycopeptide antibiotics, vancomicin and teicoplanin, are commonly considered first-line antibiotics for the treatment of coagulase-negative staphylococcus and staphylococcus aureus. Vancomycin, although effective, is associated with a high incidence of anaphylactic reactions (red man syndrome), renal and/or ototoxicity, especially when given in conjunction with aminoglycosides (7, 22). Teicoplanin, which is a newer glycopeptide antibiotic and has many advantages over vancomycin. There are few data available on teicoplanin therapy in neonatal sepsis (7, 20, 22).

On the basis of results of repeat-dose trials and pharmacokinetic studies, the current recommended dosage of teicoplanin in neonates (loading dose 16 mg/kg on the first day followed by 8 mg/kg daily) ensures trough serum teicoplanin concentration > 10 mg/dl. This is above the MIC of common pathogens (20). Vancomycin is administered by slow intravenous infusion in large volumes of diluents while teicoplanin is administered as an intravenous bolus or intramuscular injection, thus requiring a smaller volume of diluents. The administration of teicoplanin intravenously or intramuscularly does not give statistically different plasma concentrations. Yalaz et al. (24) administered teicoplanin intramuscularly to 10 neonates (median age 4 days) after the intravenous treatment of this drug without any problems. Vancomycin does not share this advantage, which increases patient comfort and increased cost. Yalaz et al. (24) reported a mortality of 16.2% despite the study group consisting of mostly pre-term infants (86.4%), and was 27.2% and 11.5% in neonates with Streptococcus aureus and coagulase-negative streptococcus sepsis, respectively. In a recent review, the mean mortality in neonates was 14.9 $\pm$ 24.5% because of methicillin-resistance Streptococcus aureus (26). Stoll et al. (19) reported 9.1% mortality in neonates with coagulase-negative sepsis, while in another study it was 17.24% (27). Neonates had been reported to have a low incidence of adverse events related to teicoplanin treatment when compared to vancomycin (7, 20).

Teicoplanin was well tolerated in newborns with acute renal failure even when given in excessive dosage (28). Teicoplanin, similar to vancomycin, does not cause severe hepatic toxicity in adult patients (22). In a recent review, the mean mortality in neonates was 14.9 $\pm$ 24.5% because of methicillin-resistant Staphylococcus aureus (26). Degraeuwe et al. (20) did not find evidence of teicoplanin nephrotoxicity including serum creatinine and alternate in creatinine clearance, in preterm neonates. Yalaz et al. (24) did not find any signs of nephrotoxicity based on creatinine concentration and calculated glomerular filtration rate. Teicoplanin was well tolerated in the newborn with acute renal failure. The only variations in biochemical values observed in neonates by Yalaz et al. (24) was an elevated concentration of

serum albumin, total bilirubin and alkaline phosphatase (**Table.6**). In neonatal medicine, patients with caused methicillin-resistant staphylococci are commonly treated with vancomicin. Teicoplanin, a newer glycopeptide antibiotic, represents an interesting alternative (29). Comparative studies in adult patients have demonstrated that teicoplanin is equally effective and associated with fewer side effects than vancomycin (20).

Coagulase-negative staphylococci are among the most frequently isolated microorganisms in clinical microbiological laboratories (30). A large proportion of nosocomial isolated coagulase-negative staphylococci are resistant to multiple antibiotics, including penicillinase-resistant penicillins (31). Given the extremely high frequency of these isolates, vancomycin has been recommended empirically for the treatment of infections by these microorganisms (31-33). Until recently, coagulase-negative staphylococci have displayed uniform susceptibility to glycopeptides; however, the emergence of strains with decreased levels of susceptibility to vancomycin and teicoplanin has been noticed in several studies (34-42).

A total of 4,458 Staphylococcus epidermis and 1,355 other coagulase-negative staphylococci were isolated at the University General Hospital Ggregorio Maranon in Madrid in the period from January 1991 to December 1995 (30). The total number of isolates was 5,813. The distribution of teicoplanin resistant among staphylococci is summarized in **Table.7**. During the same period, a total of 7,739 Staphylococcus aureus strains were isolated, and all were susceptible to both teicoplanin and vancomycin. Twenty-nine of isolates (90.6%) were also methicillin resistant, 26 (81.2%) were gentamicin resistant, 7(21.8%) were resistant to trimethoprin- sulfamethoxole, and all were susceptible to vancomycin; 81% of the coagulase-negative staphylococci were resistant to more than 10 antimicrobial agents (30). The percentage of no susceptible coagulase-negative staphylococci to teicoplanin was 0.5%.

3-4. Pharmacokinetics of teicoplanin in neonates and children

Very little is known about the pharmacokinetics of teicoplanin in neonates. Sanchez et al. (43) reported the pharmacokinetics of teicoplanin in 21 children aged from 7 days to 12 years. Seven patients were younger than 3 months, and 7 patients were older than 12 months. The patients weighed between 2.7 and 40 kg (mean 8.1 $\pm$ 9.3 kg).

Teicoplanin administration was started because of sepsis in 10 patients and pneumonia in eight. No patients presented alteration of hepatic function before treatment. Pharmacokinetic analysis demonstrated that the model that best represented the data was the open biocompartmental model. The area under the curve (AUC) was 224.5 mg/LH, the distribution volume at steady-state was 1.02 l/kg, the mean residence time was 22.9 hours, total clearance was 45 ml/kg/h, peak concentration was 26.2 µg/ml, trough concentration was 5.8 µg/ml, mean concentration at steady-state (AUC/dose interval) was 9.4 µg/ml and terminal disposition half-life was 17.4 hours. Few studies have been carried out on the pharmacokinetics of teicoplanin in children. Reed et al. (44) reported the pharmacokinetics of teicoplanin in 12 children aged from 2.4 to 11 years. Six mg/kg of teicoplanin was administered by intravenous infusion over 20 to 30 min. Three -compartment pharmacokinetic analysis was used to describe the drug's disposition characteristics. Peak and 4 hours trough serum teicoplanin concentrations averaged 39.3 and 1.8 µg/ml after the first dose with little accumulation observed after 5 days of

therapy. Teicoplanin disposition was variable: the distribution volume at steady-state ranged from 0.31 to 0.68 l/kg. The elimination half-life ranged from 6.5 to 18.1 hours and the clearance ranged from 1 to 29 ml/h/kg. Teicoplanin administration was well tolerated by all study subjects. Using the teicoplanin pharmacokinetic data by Reed et al. (44), a dose of teicoplanin of 8 mg/kg administered every 12 hours should achieve target serum trough concentrations averaging 11 µg/ml.

Tarral et al. (45) studied the pharmacokinetics of teicoplanin in 6 children aged from 4 to 12 years (mean, 7 years) and in 4 full term neonates aged from 3 to 25 days (mean, 8.5 days) weighing from 3.2 to 3.8 kg (mean, 3.26 kg). A single dose of 6 mg/kg was infused intravenously in 10 min. In neonates, the median residence time was 34.76 hours, the median AUC was 389.87 µg/h/ml, the median distribution volume at steady-state was 0.595 l/kg, the median elimination half-life was 27.42 hours, the median elimination constant was 0.047 $hours^{-1}$, and the median trough concentration was 2.04 µg/ml. In children, the median trough serum concentration is too low when compared with the MIC of teicoplanin for some sensitive organisms. The most satisfactory dose would be 10 mg/kg/day in children and 6 mg/kg/day in neonates. Using a dose of 6 mg/kg/day in neonates the peak level would range from 12.52 µg/ml on the first day to 26.92 µg/ml at steady-state, and the trough level would range from 6.10 to 14.74 µg/ml, respectively. Terragna et al. (46) studied the pharmacokinetics of teicoplanin in 13 male children aged from 2 to 12 years. Blood and urine samples were collected for 8 days after administration. Patients were given a single 3-mg/kg intravenous dose of teicoplanin for prophylaxis. Pharmacokinetic parameters were estimated from a three -compartment open pharmacokinetic model and from a noncompartmental analysis. The levels in plasma 1 hour after the administration averaged 14.8 µg/ml. The half-lives of the two distribution phases were 1.3 and 9.7 hours and the half-life of the terminal phase averaged 57.9 hours. The distribution volume of the central compartment was 0.15 l/kg, whereas the distribution volume at steady-state and during the elimination phase were 0.80 and 1.25 l/kg, respectively.

The total body teicoplanin clearance averaged 14.8 ml/h/kg, with renal clearance accounting for about 60% of the dose. The average cumulative recovery of teicoplanin in urine over 8 days was 59%, similar to the value obtained in adult volunteers. There was no significant linear correlation between elimination half-life and age. Preliminary data after repeated administration support the reliability of the model used and validity of the mean estimated parameters. There were no local or systematic adverse reactions to teicoplanin.

Table-1: Teicoplanin trough concentrations on day 3 or 4 after loading dose administration; the figures are the median and range, by Yamada et al. (15)

Loading dose	Trough concentration µg/ml	Total (n=24)	Day 3 <15 µg/ml (n=8)	Day 3 ≥15 µg/ml (n=5)	Day 4 (<15 µg/ml (n=3)	Day 4 ≥15/mg/ml (n=8)
>16-24 mg/kg on day 1, followed by >8-12 mg/kg q24 h	24.2 (22.7-25.7)	2	0	2	0	0
>12-16 mg/kg on day 1, followed by >6-8 mg/kg q24 h	19.6 (8.3-28.3)	8	2	2	1	3

>8-12 mg/kg on day 1, followed by >4-6 mg/kg q24h	16.2 (6.0-27.5)	10	3	1	1	5
>4-8 mg/kg on day 1, followed by >2-4 mg/kg q 24h	7.0 (3.8-12.6)	4	3	0	1	0

Q24= every 24 hours.

Table-2: Incidence of adverse reactions in neonates treated with teicoplanin, overall and by teicoplanin trough concentration, by Yamada et al. (15).

Variables	Total (%)	<20 µg/ml (%)	≥ 20 µg/ml	p-value
Hepatic dysfunction	4.27 (14.8)	3/17 (17.6)	1/10 (10.0)	0.523
Renal impairment	5/25 (20%)	2/15 (13.3)	3/10 (30.0)	0.301
Thrombocytopenia	4/27 (14.8)	4/17 (23.5)	0/10 (0.0)	0.136

Table-3: Demographic characteristics of the neonates admitted to the neonatal intensive care unit between January 2000 and December 2002 who had staphylococcal septicemia, by Yalaz et al. (24); the figures are the Mean + SD (range).

Variables	All episodes of staphylococcal septicemia (n=37)	Episodes of septicemia due to Staphylococcus aureus (n=11)	Episodes of septicemia due to coagulase-negative staphylococci (n=26)	P-value
Gender (female/male)	15/22	4/7	11/15	NS
Gestational age	34.2±2.3	32.1±2.0	15.1±3.3	<0.001
No (%) of neonates with gestational age < 37 weeks	32 (86.5)	11 (100)	35.1±33	<0.05
Birth weight	2,064±677	1,520±405	2,320±548	<0.05
No (%) of neonates with birth weight < 2,500	27 (73.0)	11 (100)	16 (61.5)	<0.05
No (%) delivered by caesarian section	20 (54.5)	6 (54.5)	14 (53.8)	NS

NS: Not significant; SD: Standard Deviation.

Table-4: Risk factors for staphylococci septicemia and outcomes of Teicoplanin treatment in neonates admitted to the neonatal intensive care unit between January 2000 and December 2002, by Yalaz et al. (24); the figures are the Mean ± SD (range).

Variables	All episodes of staphylococci septicemia (n=37)	Episodes of septicemia due to Staphylococcus aureus (n=11)	Episodes of septicemia due to coagulase-negative staphylococci (n=26)	P-value
Time to diagnosis of sepsis*	5; 6.4±3.0	5; 4.6±3.0	5; 9.2±4.6	<0.001
No (%) of neonates				
With at least two clinical findings	31 (83.8)	8 (72.7)	23 (88.5)	NS
Requiring at least 3 days of Teicoplanin	35 (94.5)	10 (91.0)	25 (96.2)	NS
Requiring central venous catheterizing	22 (59.5)	8 (72.7)	14 (53.8)	<0.01
Requiring at least 3 days of mechanical ventilation	22 (59.5)	10 (91.0)	12 (46.2)	<0.01

With meningitis	0	0	0	NS
Bacteriological cure rate all patients (%)	33 (89.2)	9 (81.8)	24 (92.3)	NS
Mortality (%)	6 (16.2)	3 (27.3)	3 (11.5%)	P<0.01
Surviving infants (%)				
Bacteriological cure rate	31 (100%)	8 (100)	23 (100)	NS
*Time to bacteriological cure	6; 4.8±1.6	6; 5.3±1.3	6; 4.1±0.1	NS
Of surviving infants (days)	(2-9)	(2-9)	(2-9)	NS
Duration of treatment*	12; 11.6±2.3 (7-15)	12; 11.8±2.3 (7-15)	10; 9.8±2.8 (7-14)	NS

*Figures are median; Mean ± SD (range); NS: Not significant.

Table-5: Laboratory findings in neonates admitted to the neonatal intensive care unit between January 2000 and December 2002 diagnosed with staphylococcus septicemia, by Yalaz et al. (24); the figures are the number of neonates and (%).

Variables	All episodes of staphylococcal septicemia (n=37)	Episodes of septicemia due to Staphylococcus aureus (11)	Episodes of septicemia do coagulase-negative staphylococci (n=26)	P-value
Leucopenia (<5,000/mm^3)	8 (21.6)	3 (27.3)	5 (19.2)	NS
Leucocytosis (<100,000/mm^3)	14 (37.8)	5 (45.5)	9 (34.6)	NS
Thrombocytopenia (<100,000 mm^3)	22 (59.5)	7 (63.6)	15 (57.7)	NS
C-reactive protein (>0.34 mg/dl)	30 (81.1)	7 (63.6)	23 (88.5)	<0.05
Hypoglycemia (<40 mg/dl)	22 (59.5)	8 (72.7)	14 (53.8)	<0.05
Hyperglycemia (>150 mg/dl	12 (32.4)	4 (36.4)	8 (30.8)	NS
Metabolic acidosis	14 (37.8)	7 (63.6)	7 (26.9)	NS

NS: Not significant.

Table-6: Laboratory parameters reflecting hepatic and renal function before and after teicoplanin treatment in the 31 neonates with staphylococcal sepsis who survived, by Yalaz et al. (24); the figures are the Mean ± SD.

Parameters	Before treatment	After treatment	P-value
Blood urea nitrogen (mg/dl)	16.6±5.8	16.2±3.88	NS
Creatinine (mg/dl)	0.70±0.27	0.72±0.17	NS
Aspartate aminotransferase (U/l)	61.5±20.5	53.6±19.0	NS
Alanine aminotransferase (U/l)	49.0±29.1	54.1±14.4	NS
Total bilirubin (mg/dl)	9.25±3.21	13.0±4.20	<0.05
Direct bilirubin (mg/dl)	1.02±0.3	1.07±02	NS
Alkaline phosphatase (UI)	540.3±145.6	615.4±187.9	NS
γ-Glutamyl transferase (U/I)	65.4±17.5	87.8±15.2	<0.05
Albumin (g/dl)	2.6±0.4	2.9±0.8	<0.05
Glomerular filtration (ml/min)	48±5.1	51±8.2	NS

Table-7: Distribution of Teicoplanin resistance among staphylococci isolated in the University General Hospital Gregorio Maranon in Madrid from January 1991 to December 1995, by Cercenado et al. (30).

Strain	Total number of strains	No. of Teicoplanin-resistance strains from:	
		Infected patients	Colonized patients
Staphylococcus aureus	7,739	0	0
Staphylococcus epidermidis	4,458	3	11
Other coagulase-negative staphylococci	1,355	11	7
Total	13,552	14	18

4-DISCUSSION

Teicoplanin is a useful glycoside antibiotic with similar antimicrobial activity to vancomycin, but has some advantages in that it only needs to be given once a day, and does need to be given as slowly as vancomicin and can be given by intramuscular injection. Vancomycin is administered by slow intravenous infusion in large volumes of diluents while teicoplanin is administered as an intravenous bolus or intramuscular injection, thus requiring smaller volume of diluents. The administration of teicoplanin intravenously or intramuscularly does not give statistically different plasma concentrations.

Vancomycin-resistant microorganisms are sometimes sensitive to teicoplanin. Teicoplanin is a complex of five related glycopeptide antibiotics with similar properties to vancomycin. Teicoplanin was first isolated in 1976 (1). Teicoplanin is active against many gram-positive anaerobes and is particularly potent against Clostridium species. It is also active against most Listeria, enterococci and staphylococci, including methicillin-resistant strains (1). By inhibiting bacterial cell synthesis teicoplanin may work more as a bacteriostatic drug than as a bactericidal drug. Teicoplanin inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-Alanyl-D-alanine terminus of cell wall precursor units. Because of the large molecular size, glycopeptides are unable to penetrate the outer membrane of gram-negative bacteria. Teicoplanin has a large distribution volume and a long half-life and a loading dose is necessary to achieve target drug concentration shortly after administration. In neonates < 1 month old a loading dose of 16 mg/kg followed by a daily maintenance dose of 8 mg/kg is recommended (1). It is commonly suggested that the trough concentration of teicoplanin concentration ≥ 20 μg/ml is used to treat deep-seated infections such as endocarditis, bone and join infections, and osteomyelitis (10,11). Ueda et al. (22) suggested achieving a trough teicoplanin concentration ≥ 15 μg/ml and a trough concentration of 15-30 μg/ml was recommended as the new trough target. However, there is little information regarding dosage and subsequent trough concentrations of teicoplanin in neonates (7), and there are no data on either loading, and maintenance doses for the anti-methicillin-resistant Staphylococcus aureus efficacy of teicoplanin. In adults, the hepatotoxicity and thrombocytopenia occur at Teicoplanin concentrations of > 60 μg/ml, and >40 μg/ml, respectively (13). Teicoplanin is well tolerated and the incidence of hepatic dysfunction, renal impairment and thrombocytopenia is 14.8%, 20%, and 14%, respectively, when

the concentration of teicoplanin ranges from < 20 µg/ml and ≥ 20 µg/ml. The results of the analysis of the loading dose and the subsequent concentration showed that the median trough concentration in the loading dose regimen > 12-16 mg/kg on day 1, followed by > 6-8 mg/kg every 12 hours was 19.6 µg/ml (12). The corrected gestational age, serum creatinine and body weight are important factors that correlate with individual estimates of teicoplanin clearance in neonates. The teicoplanin trough concentration after administering the loading dose increases in premature infants and depends both on body weight and renal function. In the maintenance dose regimen > 6-8 mg/kg every 24 hours, the median trough concentration was 18.5 µg/ml. Staphylococcus aureus and coagulase-negative staphylococci represent the most frequent isolated nosocomial pathogens from neonates in neonatal intensive care unities (7, 20). These microorganisms show significant resistance to methicillin and/or aminoglycosides, which may be as high as 70-90%, thus glycopeptide antibiotics are used in many neonatal intensive care units (4, 19-21).

Vancomycin is a glycoside antibiotic that has been used in the neonatal care unities for many years despite its side-effects. Teicoplanin, another glycoside antibiotic, has similar clinical efficacy, but fewer side-effects compared with vancomycin and has become the preferred antibiotic (7, 22). The glycoside antibiotics, vancomycin and teicoplanin, are commonly considered first-line antibiotics for the treatment of coagulase-negative staphylococcus and staphylococcus aureus. Vancomycin, although effective, is associated with a high incidence of anaphylactic reactions (red man syndrome), renal and/or ototoxicity, especially when given in conjunction with aminoglycosides (7, 20, 22). The current recommended dosage of teicoplanin in neonates (loading dose 16 mg/kg on the first day followed by 8 mg/kg daily) ensures trough serum teicoplanin concentration > 10 mg/dl. This is above the MIC of common pathogens (20). There are different percentages of mortality due to teicoplanin. Yalaz et al. (24) reported a mortality of 16.2% despite the study group consisting of mostly preterm infants (86.4%) and was 27.2% and 11% in neonates with Streptococcus aureus and with and coagulase-negative streptococcus sepsis, respectively. Kitajima (26) reported a mortality of 14.9± 24.5 because of methicillin-resistance Streptococcus aureus and Stoll et al. (19) reported a mortality of 9.1% in neonates with coagulase-negative sepsis, while in another study the mortality was 17.24% (27). Neonates had been reported to have a low incidence of adverse events related to teicoplanin than vancomycin treatment (7, 20). Teicoplanin was well tolerated in newborns with acute failure even when given in excessive dosage.

A large proportion of nosocomial isolated coagulase-negative staphylococci are resistant to multiple antibiotics, including penicillinase-resistant penicillins (31). Given the extremely high frequency of these isolated staphylococci, vancomycin has been recommended empirically for the treatment of infection by these microorganisms (31-33). The emergence of strains with decreased levels of susceptibility to vancomycin and teicoplanin has been reported in several studies (34-42). Teicoplanin is bound to plasma proteins at a percentage of 90-95. The half-life of teicoplanin is 100 hours in adults and $2^{1/2}$ days in infants (1). Very little is known about the pharmacokinetics of teicoplanin in neonates and to our best knowledge only one article has been reported on the pharmacokinetics of teicoplanin in 4 full term neonates aged from 3 to 25 days (mean, 8.5 days) ([45). A single dose of 6 mg/kg was infused intravenously. The median residence time

was 34.76 hours, the median AUC was 389.87 µg/h/ml, the median distribution volume at steady-state was 0.595 l/kg, the median elimination half-life was 27.42 hours. Using a dose of 6 mg/kg/day the peak level would change from 12.52 and 26.92 µg/ml at steady state, and the trough level ranged from 6.10 to 14.74 µg/ml. Sanchez et al. (43) studied the pharmacokinetics of teicoplanin in 21 children, seven were younger than 3 months. The model that best represented the pharmacokinetics of teicoplanin was the open biocompartmental. Reed et al. (44) reported the pharmacokinetics of teicoplanin in 12 children aged from 2.4 to 11 years. After an intravenous infusion of 6 mg/kg of teicoplanin, 3 compartment pharmacokinetic analysis was used to describe the drug's disposition characteristics. The peak and 4 hours trough serum teicoplanin concentrations were 39.3 and 1.8 µg/ml, respectively, after the first dose with little accumulation observed after 5 days. Teicoplanin disposition was variable, the distribution volume at steady-state ranged from 0.31 to 0.68 l/kg. The half-life and the clearance ranged from 6.5 to 18.1 hours and 1 to 29 ml/h/kg, respectively.

Terranga et al. (46) studied the pharmacokinetics of teicoplanin in 13 male children aged from 2 to 12 years. A dose of 3 mg/kg of teicoplanin was administered intravenously. Pharmacokinetic parameters were estimated from a three-compartment model. The level at 1 hour after the administration was 14.8 µg/ml. The half-lives of the two distribution phases were 1.3 and 9.7 hours and the half-life of the terminal phase was 57.9 hours. The distribution volume of the central compartment was 0.15 l/kg, whereas the distribution volume at steady-state and during the elimination phase were 0.80 and 1.25 l/kg, respectively. The total body teicoplanin clearance was 14.8 ml/h/kg, with renal clearance accounting for about 60% of the dose. The average cumulative recovery of teicoplanin in urine over 8 days was 59%, similar to the value obtained in adults.

5-CONCLUSION

In conclusion, Teicoplanin is a glycoside antibiotic with similar antibacterial properties to vancomycin but Teicoplanin does not have the side-effects that vancomycin has. Teicoplanin is active against anaerobes gram-positive bacteria and is particularly potent against clostridium species. Teicoplanin is also active against most Listeria, enterococci and staphylococci including methicillin-resistant strains, nonviridans and viridans streptococci and Streptococcus pneumoniae. Teicoplanin may be active against bacteria resistant to vancomicin. Teicoplanin has been used to treat bone and join infections, osteomyelitis and endocarditis caused by methicillin-resistant and susceptible staphylococci, streptococci, and enterococci. Teicoplanin may be administered intravenously as a bolus or intramuscularly but cannot be administered orally. Teicoplanin is not metabolized and is excreted unchanged in the urine. This drug has a long half-life and a large distribution volume and thus requires the administration of a loading dose to achieve target trough concentrations shortly after the administration. In neonates, the loading dose is 16 mg/kg and the maintenance dose is 8 mg/kg, and the target trough concentration is 15-30 µg/ml.

Teicoplanin is well tolerated and the hepatic dysfunction, renal impairment and thrombocytopenia range from 14% and 20% when the serum teicoplanin ranges from < 20 µg/ml and ≥ 20 µg/ml. The mortality due to teicoplanin ranges from 9.1% and 17.4% and is higher in preterm than full term infants. The pharmacokinetic parameters of teicoplanin

range in a wide interval. There is only one report on the pharmacokinetic of teicoplanin obtained in 4 full term infants aged between 3 and 25 days. After intravenously infusing 6 mg/kg teicopletinin, the elimination half-life is 27.42 hours and the distribution volume is 0.595 l/kg.

6-CONFLICT OF INTERESTS

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