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Review Article

Clinical pharmacology of teicoplanin in infants and children

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Abstract

Teicoplanin is a glycopeptide and is a mixture of related glycopeptides. 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 its large molecular size, teicoplanin is unable to penetrate the outer membrane of gram-negative bacteria. The intravenous dosage of teicoplanin consists in a loading dose of 16 mg/kg followed by a maintenance dose of 8 mg/kg once-daily to infants aged < one month and in older infants the dosage of teicoplanin consists in a loading dose of 12 mg/kg twice-daily followed by a maintenance dose of 10 mg/kg once daily. In children, the oral dose is 100 to 200 mg twice-daily and the intravenous dosage consists in 12 mg/kg twice-daily followed by 12 mg/kg once-daily. Teicoplanin has been found efficacy and safe in infants and children. The elimination half-life of teicoplanin is 73.9 hours in infants and children and teicoplanin is cleared from the body by renal and extra-renal routes. The total body clearance of teicoplanin is 0.09 L/h in children aged < 12 months and 0.29 L/h in older children. The treatment and the prophylaxis with teicoplanin have been described in infants and children. Teicoplanin administered intravenously and/or intraventricularly treats the cerebral infections caused by staphylococci and enterococci. The aim of this study is to review the published data on teicoplanin dosing, efficacy and safety, pharmacokinetics, drug-interactions, treatment, prophylaxis, and penetrates into the cerebrospinal fluid in infants and children.

Key words: teicoplanin, dosing, efficacy, safety, pharmacokinetic, treatment, cerebrospinal fluid, infants, children

Running title: teicoplanin in infants and children.

Introduction

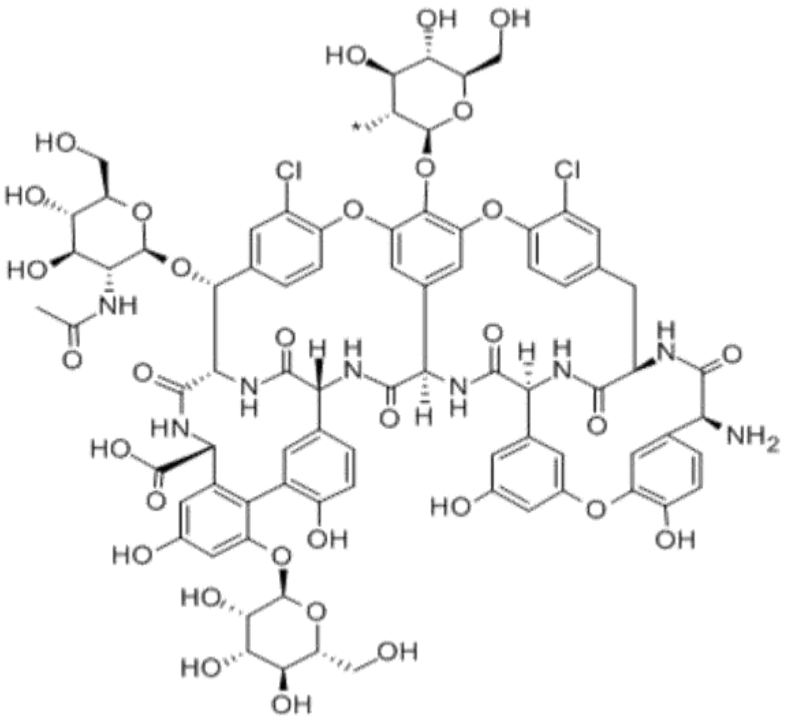
Teicoplanin is a glycopeptide and is a mixture of related glycopeptides. It is similar to vancomycin in chemical structure, mechanism of action, spectrum of activity, and route of elimination which is primarily renal [1].

Mechanism of action of teicoplanin

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 its large molecular size, teicoplanin is unable to penetrate the outer membrane of gram-negative bacteria [1].

Absorption, distribution metabolism and elimination of teicoplanin

Teicoplanin may be administered by intramuscular injection as well as by intravenous administration. An intravenous dose of 1 gram in adults produces plasma concentrations of 15 to 30 µg/ml 1 hour after 1 to 2 hours of infusion. Teicoplanin is highly bound by plasma proteins (90 to 95%) and has extremely long serum elimination; the half-life is up to 100 hours allowing for once-daily dosing. Excretion is though glomerular filtration [1].



Molecular structure of teicoplanin (molecular weight = 1879.7 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "teicoplanin dosing infants, children", teicoplanin efficacy, safety infants, children", "teicoplanin pharmacokinetics infants, children", "drug-interactions", "teicoplanin treatment infants, children", "teicoplanin prophylaxis infants, children", and "teicoplanin penetration into the cerebrospinal fluid". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], and The British National Formulary for Children [3] were consulted.

Results

Dosing schedules of teicoplanin in infants and children

Intravenous administration to infants [2]

Infants aged < one month. Give 16 mg/kg loading dose by intravenous injection followed by an intravenous or intramuscular maintenance dose of 8 mg/kg once-daily. Double the dosage interval in infants with renal failure.

Older infants. Give 10 mg/kg twice-daily intravenously followed by a maintenance dose of 10 mg/kg once-daily.

Oral or intravenous administration to children [3]

Oral treatment of clostridium difficile

Children aged 12 to 17 years. Give: 100 to 200 mg twice-daily for 7 to 14 days.

Intravenous or intramuscular administration for serious infections caused by gram-positive bacteria (e.g., complicated skin, soft-tissue infections, pneumonia, and complicated urinary-tract infections)

Children aged 12 to 17 years. Give: initially 12 mg/kg twice-daily for 3 to 5 days followed by a maintenance dose of 12 mg/kg once-daily.

Intravenous administration for serious infections caused by gram-positive bacteria (including endocarditis, complicated skin and soft-tissue infections, pneumonia, complicated urinary-tract infections, bone, and joint infections)

Children aged 1 month. Give initially 16 mg/kg for 1 dose, followed by a maintenance dose of 8 mg/kg once-daily.

Children aged 2 months to 11 years. Give initially 10 mg/kg twice-daily for 3 doses, followed by a maintenance dose of 6 to 10 mg/kg once-daily.

Efficacy and safety of teicoplanin in infants and children

Teicoplanin has been found efficacy and safe in treating infants with staphylococcal sepsis [4]. Teicoplanin and vancomycin are equally effective in treating bacterial infections; however the incidence of nephrotoxicity and other adverse-effects are lower with teicoplanin. It may be reasonable to consider teicoplanin for children at higher risk for acute kidney injury [5]. While vancomycin and teicoplanin exhibit equal clinical and microbiological efficacy in treating bacteraemia, teicoplanin is less likely to induce allergic reactions or nephrotoxicity in children [6]. The results of the meta-analysis indicate that teicoplanin and vancomycin are similar in both efficacy and safety, thus teicoplanin can act as an effective alternative to vancomycin for treating children infected by methicillin-resistant Staphylococcus aureus [7]. Home treatment of infections with teicoplanin is effective, well tolerated, and offers advantages in terms of quality of life in ill children [8].

Pharmacokinetics of teicoplanin in infants and children

Lukas et al. [9] studied the pharmacokinetics of teicoplanin in 40 infants and children who were aged 37.6±35.4 months and weighed 14.3±6.2 kg. Subjects were randomized to receive either 3 loading doses of teicoplanin intravenously at a dose of 10 mg/kg twice-daily followed by a maintenance dose 10 mg/kg once-daily or the same loading dose followed by a maintenance dose of 15 mg/kg once-daily. Teicoplanin was administered as 1 hour infusion.

	Typical value+SEM	%Coefficient of variation
Total body clearance (L/h)	0.23±0.12	72
Central distribution volume (L)	3.16±0.46	58
Transfer rate constant K12 (h^{-1})	0.23±0.025	26
Transfer rate constant K21 (h^{-1})	0.04±0.016	50
Peripheral distribution volume (L)	4.7±0.41	---
Absorption half-life (h)	2.0	---
Elimination half-life (h)	73.9	---

Table 1. *Teicoplanin basic compartmental population (NONMEN) parameters. Figures are the mean+SEM, by Lukas et al. [9].*

K12 = transfer rate constant from the central to peripheral compartment. K21 = transfer rate constant from the peripheral to central compartment. This table shows that the central distribution volume is larger than the water volume, K12 is greater than K21, and the absorption half-life is smaller than the elimination half-life.

	Typical value+SEM	%Coefficient of variation
Age < 12 months (N = 4)		
Total body clearance (L/h)	0.09±0.02[a]	37
Central distribution volume (L)	1.05±0.04[a]	---
Transfer rate constant K12 (h^{-1})	0.35±0.25[b]	---
Transfer rate constant K21 (h^{-1})	0.10±0.07[b]	---
Central compartment half-life (h)	8.1	---
Age ≥ 12 months to 10 years (N = 16)		
Total body clearance (L/h)	0.29±0.12	23
Central distribution volume (L)	3.9±0.51	---
Transfer rate constant K12 (h^{-1})	0.23±0.02	---
Transfer rate constant K21 (h^{-1})	0.03±0.12[b]	---
Central compartment half-life (h)	9.32	---

Table 2. *Compartmental population pharmacokinetic parameters of teicoplanin in infants, aged < 12 months, and in children aged ≥ 12 months to 10 years. Figures are the mean+SEM, by Lukas et al. [9].*

K12 = transfer rate constant from the central to peripheral compartment. K21 = transfer rate constant from the peripheral to central compartment.

[a]P-value < 0.005 (Student t test for umpired data). [b]%Coefficient of variation 95% contains zero. This table shows that the total body clearance and the central distribution volume are lower in younger than older subjects.

Reed et al. [10] investigated the pharmacokinetics of teicoplanin in 12 infants and children aged 6+3.1 years and weighed 21.4+9.3 kg. Each subject received teicoplanin intravenously at a dose of 6 mg/kg once-daily for 5 days. Teicoplanin concentration was measured in the plasma and urine.

Parameter	Day 1 of administration	Days 1 to 5 of administration
Total body clearance (ml/min/kg)	39.7±2.4	36.5+2.4
Renal clearance (ml/min/kg)	18.2±3.1	---
Clearance ratio, TBC/RC	0.51±0.07	---
Amount excreted unchanged in urine (0-24h) Fe (%dose administered)	48.6±7.1	---

Table 3. *Pharmacokinetic parameters of teicoplanin which are measured in the plasma and urine of infants and children. The figures are the mean+SEM, by Reed et al. [10].*

This table shows that teicoplanin is eliminated by both the renal route and extra-renal routes.

Ramos-Martín et al. [11] explored the pharmacokinetics of teicoplanin in 39 infants and children aged 4+4.3 years and weighed 17.3+13.3 kg. Teicoplanin was administered intravenously at a dose of 10 mg/kg twice-daily for 3 loading doses followed by a maintenance dose of 10 mg/kg once-daily.

Parameter and model	Mean	Median	SD
Standard model			
Total body clearance (L/h)	0.396	0.279	0.347
Central distribution volume (L)	4.259	2.592	3.597
Kcp (h^{-1})	3.344	0.434	7.742
Kpc (h^{-1})	4.424	0.252	9.742
Linear model			
Total body clearance $_{slope}$ (L/h/kg)	0.023	0.019	0.010
Central distribution volume (L)	4.138	2.282	4.143
Kcp (h^{-1})	3.876	0.474	8.156
Kpc (h^{-1})	3.994	0.292	8.930
Allometric model			
Total body clearance $_{std}$ (L/h/70 kg)	0.045	0.040	0.020
Central distribution volume (L)	3.447	1.975	3.579
Kcp (h^{-1})	4.897	0.564	9.054
Kpc (h^{-1})	4.227	0.228	9.638

Table 4. *Population pharmacokinetic parameters which are measured in 39 infants and children. Figures are the mean, median, and standard deviation (SD), by Ramos-Martín et al. [11].*

Kcp = first-order rate constant from the central to peripheral compartment. Kpc = first-order rate constant from peripheral to central compartment.

This table shows that the central distribution volume is larger than the water volume. The transfer rate constant from the central to peripheral compartment is similar to the transfer rate constant from the peripheral to central distribution compartment. This observation is in conflict with that reported in tables 1 and 2 where the transfer rate constant from the central to peripheral compartment is greater than the transfer rate constant from the peripheral to central comportment. There is a remarkable interindividual variability in the pharmacokinetic parameters of teicoplanin.

Interaction of teicoplanin with drugs

Teicoplanin co-administered with cefotaxime and ofloxacin has a synergist effect in gram-positive organisms [12]. A synergistic effect is observed with the combination of teicoplanin and netilmicin and amikacin in enterococci and staphylococci [13].

Treatment with teicoplanin in infants and children

Twenty-three preterm infants had the gestational age of 28.4 weeks, the postnatal age ranged from 5 to 47 days, and had a sepsis caused by staphylococci. The infection is cured with teicoplanin loading dose of 15 mg/kg followed by a maintenance dose of 8 mg/kg once-daily [14]. Of twenty-nine children with infections caused by gram-positive organisms 21 children (72.4%) are cured with teicoplanin [15]. Children, aged ≤ 18 years, had an infection caused by gram-positive organisms and are cured with teicoplanin at a dose of 10 mg/kg twice-daily [16]. Children, aged 2 to 12 years, with gram-positive infections are cured with teicoplanin at a dose 10 mg/kg daily [17]. The loading dose of teicoplanin (6 mg/kg twice-daily for at least three doses) must be considered mandatory in all children, regardless of their renal function, to enable optimal drug concentrations to be achieved early in the treatment period [18].

Prophylaxis with teicoplanin in children

Antibiotic prophylaxis with teicoplanin appears safe and feasible and eradicates viridians sepsis and decreases the incidence of febrile neutropenia in paediatric patients with acute myeloid leukaemia [19]. Prophylaxis with teicoplanin is efficacy in preventing Staphylococcal epidermidis in children [20].

Treatment of cerebral infections with intravenous and/or intraventricular teicoplanin

Teicoplanin administered intravenously at a dose of 15 mg/kg daily decreases the staphylococci and enterococci counts in the cerebrospinal fluid from 2.31% to 0.71% 6 hours after dosing, becomes bactericidal 24 hours after treatment, and this treatment does not produce therapeutic failures [21]. Teicoplanin administered intravenously at a dose of 240 mg once-daily and intraventricularly at a dose of 10 mg once-daily treats the staphylococcal ventriculitis and no signs of recurrent infection or adverse-effects were observed [22]. Seven patients with staphylococcal neurosurgical shunt infections were treated with teicoplanin intraventricularly. Two infants received 5 mg daily and five patients received 20 mg daily. Intraventricular administration of teicoplanin produces high and prolonged peak and trough levels of teicoplanin in the cerebrospinal fluid and the bactericidal activity of teicoplanin in the cerebrospinal fluid is remarkable [23]. Three patients had the cerebrospinal fluid infected by Staphylococcus epidermidis and Enterococcus faecalis and were treated with teicoplanin intraventricularly at a dose of 10 to 15 mg daily. Teicoplanin concentrations in the cerebrospinal fluid, 24 hours after intraventricular injection, exceeded 4- to 8-fold the MICs of the infecting organisms and the cerebrospinal fluid cultures rapidly became negative [24]. One patient had the neuro-shunt infected by methicillin-sensitive Staphylococcus epidermidis and two patients had the neuro-shunt infected by methicillin-sensitive Staphylococcus aureus. Teicoplanin was administered intravenously at a dose of 400 mg daily and intraventricularly at a dose of 20 mg daily to the three patients. The therapy clears the infection in one week, the concentration of teicoplanin is 30 to 38 µg/ml (mean 34). Teicoplanin administered intravenously and intraventricularly is well tolerated and does not cause adverse-effects [25].

Discussion

Teicoplanin is a glycopeptide and is a mixture of related glycopeptides. 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 its large molecular size, teicoplanin is unable to penetrate the outer membrane of gram-negative bacteria [1]. The intravenous dosage of teicoplanin consists in a loading dose 16 mg/kg followed by a maintenance dose of 8 mg/kg once-daily in infants aged < one month and in older infants the teicoplanin dosage consists in 10 mg/kg twice-daily followed by 10 mg/kg once-daily [2]. In children, the oral dose is 100 to 200 mg twice-daily and the intravenous dosage consists in a loading dose of 12 mg/kg twice-daily followed by a maintenance dose of 12 mg/kg once-daily [3]. Teicoplanin has been found efficacy and safety in infants and children [4-8]. Teicoplanin has been found efficacy in infants with staphylococcal sepsis [4]. Teicoplanin and vancomycin are

equally effective in treating children with bacterial infections but the incidence of toxicity and other adverse-effects are lower with teicoplanin [5, 6]. Teicoplanin is an effective alternative to vancomycin for treating children infected by methicillin-resistant Staphylococcus aureus [7]. The home treatment with teicoplanin is effective and well tolerated in ill children [8]. The pharmacokinetics of teicoplanin has been studied in infants and children [9-11]. In infants and children with a mean age of 37.6 months, teicoplanin was administered intravenously at a dose of 10 mg/kg twice-daily followed by a dose of 10 mg/kg once-daily. The elimination half-life is 73.9 hours and is 37-fold longer than the absorption half-life. The total body clearance is 0.23 L/h and the central distribution volume is 3.16 L thus it is larger than the water volume. The transfer rate constant from the central to peripheral compartment is higher than the transfer rate constant from the peripheral to the central compartment. The total body clearance and the central distribution volume are age-dependent. The total body clearance is 0.09 L/h and 0.29 L/h and the central distribution volume is 1.05 and 3.9 L in children aged < 12 months and in children aged ≥ 12 months to 10 years [9]. In infants and children with a mean age of 6 years, the teicoplanin total body clearance is 39.7 ml/min/kg and the renal clearance is 18.2 ml/min/kg suggesting that teicoplanin is cleared from the body by renal and extra-renal routes [10]. In infants and children with a mean age of 4 years, the mean total body clearance of teicoplanin is 0.396 L/h and the mean central distribution volume is 4.259 L. The first-order rate constant from the central to peripheral compartment is similar to that of peripheral to central compartment [11] and this result is in conflict with that previously reported by Lukas et al. [9] who found that the transfer rate constant from the central to peripheral compartment is higher than the transfer rate constant from the peripheral to central compartment. A synergistic effect is observed with the co-administration of teicoplanin with cefotaxime and ofloxacin in gram-positive organisms [12] and with the combination of teicoplanin and netilmicin and amikacin in enterococci and staphylococci [13]. The treatment with teicoplanin has been studied in infants and children [14-18]. Infants with sepsis caused by staphylococci are cured with teicoplanin at a loading dose of 15 mg/kg followed by a maintenance dose of 8 mg/kg once-daily [14]. Children with infections due to gram-positive organisms are cured with teicoplanin [15], and children with infections caused by gram-positive organisms are cured with teicoplanin at a dose of 10 mg/kg daily [16, 17]. A loading dose of teicoplanin of 6 mg/kg twice-daily for at least three doses has been recommended in children with bacterial infection [18]. The prophylaxis with teicoplanin is efficacy in eradication viridians sepsis and in decreasing the incidence of febrile neutropenia in paediatric patients [19] and prevents the infection caused by Staphylococcal epidermis in children [20]. The treatment of cerebral infections has been described in five studies [21-25]. Teicoplanin administered at a dose of 15 mg/kg daily decreases the staphylococci and enterococci counts in the cerebrospinal fluid at 6 hours after dosing and is bactericidal at 24 hours after administration [21]. Teicoplanin was administered intravenously at a dose of 240 mg once-daily and intraventricularly at a dose of 10 mg once-daily, this therapy treats staphylococcal ventriculitis, and the treatment has been found efficacy and safe [22]. Two infants and five patients with staphylococcal neurosurgical shunt infections were treated with teicoplanin intraventricularly and the treatment produces prolonged peak and through levels of teicoplanin and sterilizes the cerebrospinal fluid [23]. The intraventricular administration of teicoplanin at a dose of 10 to 15 mg daily results in 4- to 8-fold the MICs of Staphylococcus epidermidis and Enterococcus faecalis and the cerebrospinal fluid cultures begin negative [24]. One patient had the neuro-shunt infected by methicillin-sensitive Staphylococcus epidermidis and two patients had the neuro-shunt infected by methicillin-sensitive Staphylococcus aureus. The patients were treated with teicoplanin intravenously at a dose of 400 mg daily and intraventricularly at a dose of 20 mg daily and this treatment is effective, well tolerated, and does not produce adverse-effects [25].

In conclusion, teicoplanin is a glycopeptide and is a mixture of related glycopeptides. Teicoplanin inhibits the synthesis of the cell wall precursor units. Because of its large molecular size, teicoplanin is unable to penetrate the outer membrane of gram-negative bacteria. The intravenous dosage of teicoplanin consists in 16 mg/kg loading dose followed by a maintenance dose of 8 mg/kg once-daily to infants aged < one month. In older infants, the teicoplanin consist is a loading dose is 10 mg/kg twice-daily followed by a maintenance dose of 10 mg/kg once-daily. In children the oral dose is 100 to 200 mg twice-daily and the intravenous dosage consists in a loading dose of 12 mg/kg twice-daily followed by a maintenance dose of 12 mg/kg once-daily. In infants and children with a mean age of 37.6 months, the teicoplanin elimination half-life, the total body clearance and the central distribution volume are 73.9 hours, 0.23 L/h, and 3.16 L, respectively, and the total body clearance and the central distribution volume are age-dependent being lower in children aged < 12 months than in children aged ≥ 12 months to 10 years. The treatment and the prophylaxis with teicoplanin have been studied in infants and children. Teicoplanin treats the sepsis caused by staphylococci and by gram-positive organisms. Prophylaxis with teicoplanin treated viridians sepsis and prevented infection caused by Staphylococcus epidermis. Teicoplanin administered intravenously and/or intraventricularly treats the cerebral infections caused by staphylococci and enterococci. The aim of this study is to review the clinical pharmacology of teicoplanin in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria. This article is a review and drugs have not been administered to men or animals.

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