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Research Article

Clinical Pharmacology of Trimethoprim-Sulfamethoxazole in Paediatric Patients

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Abstract:

Trimethoprim-sulfamethoxazole is the sulphonamide used in paediatric patients. Trimethoprim-sulfamethoxazole is available as a single-entity preparation and its introduction in clinic has been an important advance in treatment of bacterial infections. Trimethoprim inhibits bacterial dihydrofolate reductase an enzyme downstream form the one that sulphonamides inhibit in the same biosynthetic sequence. This formulation consists in a ratio of sulfamethoxazole:trimethoprin 20:1, may be bactericidal, and in-vivo concentration of sulfamethoxazole is 20-times greater than that of trimethoprim. Trimethoprim-sulfamethoxazole is active against most strains of Staphylococcus aureus and Staphylococcus epidermis, even among methicillin-resistant isolates, viridians group of streptococci, Escherichia coli, Proteus mirabilis, Klebsiella and Enterobacter species, Salmonella, Pseudomonas pseudomallei, Serratia species, Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Yersinia enterocolitica, and Nocardia asteroides. Trimethoprim-sulfamethoxazole has been found efficacy and safe in children but may induce adverse-effects. Both trimethoprim and sulfamethoxazole are rapidly absorbed following oral administration and their absorption-rate constant is 1.27 and 0.58 h-1, respectively. Trimethoprim and sulfamethoxazole inhibits CYP2C8 and CYP2C9, respectively. Prophylaxis and treatment with trimethoprim-sulfamethoxazole have been reviewed and this drug combination treated the meningitis caused by Listeria monocytogenes, Elizabethkingia, Nocardia meningitis, Elizabethkingia meningoseptica, and Staphylococcus aureus. Trimethoprim and sulfamethoxazole are poorly transferred across the human placenta and poorly migrate into the breast-milk. The aim of this study is to review trimethoprim-sulfamethoxazole dosing, efficacy and safely, adverse-effects, interaction with drugs, prophylaxis, treatment and treatment of bacterial meningitis and trimethoprim and sulfamethoxazole pharmacokinetics, penetration into the cerebrospinal fluid, transfer across the human placenta, and migration into the breast-milk.

Keywords: adverse-effects; cerebrospinal-fluid; children; dosing; efficacy-safely; infants; meningitis; pharmacokinetics; prophylaxis; treatment; trimethoprim-sulfamethoxazole

Introduction

Trimethoprim-sulfamethoxazole, also known as co-trimoxazole, is the sulphonamide used in paediatric patients. The combination of trimethoprim with sulfamethoxazole is available as a single-entity preparation and trimethoprim-sulfamethoxazole is an important advance in the development of clinically effective and synergistic antimicrobial agents. Trimethoprim-sulfamethoxazole is formulated to have 20-fold higher dose of sulfamethoxazole than trimethoprim. Co-trimoxazole may be administered orally or intravenously, the oral dose in infants is 120 mg/kg twice-daily, and is 240, 480, and 960 mg twice-daily in children aged up to 5, 6 to 11 and 12 to 17 years, respectively. Trimethoprim and sulfamethoxazole are potent inhibitors of CYP2C8 and CYP2C9, respectively, and these drugs are rapidly absorbed following oral administration. Trimethoprim-sulfamethoxazole interacts with drugs, the prophylaxis with trimethoprim-sulfamethoxazole prevents infections caused by different bacteria, and trimethoprim-sulfamethoxazole treats different bacterial infections. Trimethoprim and sulfamethoxazole penetrate into the cerebrospinal fluid in significant amounts, trimethoprim-sulfamethoxazole treats the bacterial meningitis, and trimethoprim and sulfamethoxazole are poorly transferred across the human placenta and poorly penetrate into the breast milk [1].

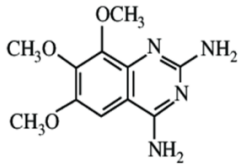
Mechanism of action of trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole is a useful antimicrobial drug but must be used when other antibiotics such as penicillins and cephalosporins cannot be employed. The antimicrobial activity of the combination of trimethoprim and sulfamethoxazole results from actions on sequential steps of the enzyme pathway for the synthesis of tetrahydrofolic acid. Tetrahydrofolate is essential for one-carbon transfer reactions (e.g., the synthesis of thymidylate from deoxyuridylate). Mammalian cells use preformed folates from the diet and do not synthesize these compounds. Furthermore, trimethoprim is a highly sensitive inhibitor of dihydrofolate reductase of lower organisms. About 100,000-times more drug is required to inhibit human dihydrofolate reductase than the bacterial enzyme. The optimal ratio of the combinations of the two agents equals the ratio of the MICs of the drugs acting independently. Although this ratio varies from

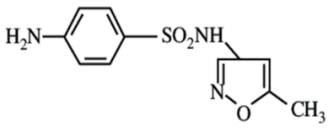
different bacteria, the most effective ratio for the greatest number of microorganisms is 20:1, sulfamethoxazole: trimethoprim. This combination is thus formulated to achieve a sulfamethoxazole concentration in-vivo that is 20-times greater than that of trimethoprim; sulfamethoxazole has pharmacokinetic properties such that the concentrations of the two drugs will thus be relatively constant in the body over a long period. Although each agent alone usually exerts bacteriostatic activity, when the organism is sensitive to both agents, bactericidal activity may be achieved [1].

Antimicrobial activity of trimethoprim-sulfamethoxazole

Although most Streptococcus pneumoniae are susceptible, there has been a disturbing increase in resistance (paralleling the rise in penicillin resistance), and its value for empiric therapeutic use in respiratory-tract infections is questionable. Most strains of Staphylococcus aureus and Staphylococcus epidermis remain susceptible, even among methicillin-resistant isolates, although geographic variation exists. Streptococcus pyogenes is usually sensitive when proper testing procedures (media with low thymidine content) are followed. The viridians group of streptococci is typically susceptible, although susceptibility among penicillin-resistant strains is low. Susceptibility in Escherichia coli varies by geographic region, although it has been declining in general. Proteus mirabilis, Klebsiella species, Enterobacter species, Salmonella, Pseudomonas pseudomallei, Serratia and Alcaligenes species are typically susceptible. Also sensitive are Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Yersinia enterocolitica, and Nocardia asteroides [1].



Trimethoprim



Sulfamethoxazole

Figure 1: *(A) Molecular weight of trimethoprim = 290.32 grams/mole (B) Molecular weight of sulfamethoxazole = 253.28 grams/mole.*

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "co-trimoxazole dosing infants, children", "trimethoprim-sulfamethoxazole efficacy, safely infants, children", "trimethoprim-sulfamethoxazole adverse-effects infants, children", "trimethoprim and sulfamethoxazole pharmacokinetics infants, children", "trimethoprim and sulfamethoxazole metabolism", "trimethoprim-sulfamethoxazole drug interactions", "trimethoprim-sulfamethoxazole prophylaxis infants, children", "trimethoprim-sulfamethoxazole treatment infants, children", "trimethoprim-sulfamethoxazole CSF infants, children", "trimethoprim-sulfamethoxazole meningitis infants, children" "trimethoprim-sulfamethoxazole placental transfer", and "trimethoprim-sulfamethoxazole breast-milk". In addition, the book "The Pharmacological Basis of Therapy" [1] has been consulted.

Treatment of infants and children with co-trimoxazole [2]

Oral treatment of susceptible infections with co-trimoxazole in infants

Infants aged 6 weeks to 5 months. Give: 120 mg twice-daily, alternatively 24 mg/kg twice-daily.

Oral treatment of susceptible infections with co-trimoxazole in children

Children aged 6 months to 5 years. Give: 240 mg twice-daily, alternatively 24 mg/kg twice-daily.

Children aged 6 to 11 years. Give: 480 mg twice-daily, alternatively 24 mg/kg twice-daily.

Children aged 12 to 17 years. Give: 960 mg twice-daily.

Treatment of susceptible infections with oral or intravenous co-trimoxazole in children

Children aged 6 weeks to 17 years. Give: 18 mg/kg twice-daily; increase the dose to 27 mg/kg twice-daily (maximum per dose = 1.44 grams). Increase the dose in severe infections.

Oral or intravenous treatment of Pneumocystis Jirovecil (Pneumocystis carinii) (undertaken where facilities for appropriate monitoring are available) in children

Children. Give: 120 mg/kg daily in 2 to 4 divided doses for 14 to 21 days. The oral route is preferable for children. Consult a microbiologist.

Oral prophylaxis of Pneumocystis Jiroveci (Pneumocystis carinii) infections with co-trimoxazole in children

Children. Give: 450 mg/m^2 twice-daily (maximum per dose = 960 mg twice-daily) for 3 days of the week (either consecutively or on alternate days).

Efficacy and safely of trimethoprim-sulfamethoxazole in children

Trimethoprim-sulfamethoxazole is an efficacy and safe treatment of Plasmodium falciparum malaria in children and effectively prevents the malaria caused by Plasmodium falciparum in children [3]. Co-trimoxazole was administered orally at a dose of 16.4 mg/kg for 26 to 59 days to 20 children, aged 9 months to 17 years, suffering from osteomyelitis. Only 8 children (40.0%) had mild adverse-effects, and co-trimoxazole effectively and safely treated osteomyelitis [4]. Seventy-six children, aged 6 months to 13 years, with acute urinary-tract infections were treated with trimethoprim-sulfamethoxazole at a dose of 8/40 mg/kg daily. No treatment failures were observed, mild adverse-effects appeared in only 16.1% of children, and this treatment effectively and safely treated urinary-tract infection [5]. Three-hundred-thirty-four children had no-obstructed urinary-tract infection, 167 children (50.0%) had vesico-ureteric reflux and 27 children (8.1%) had renal scarring. These children were treated with trimethoprim-sulfamethoxazole and neither an increase in recurrent infections was observed nor a significant modification of therapy occurred and trimethoprim-sulfamethoxazole effectively and safely treated urinary-tract infection, vesico-ureteric reflux, and renal scarring [6]. Twenty children suffering from pneumonitis caused by Pneumocystis carinii were treated with 20 mg/kg of trimethoprim and 100 mg/kg sulfamethoxazole daily and the treatment effectively and safely treated the pneumonitis [7].

Adverse-effects caused by trimethoprim-sulfamethoxazole in children

Two-hundred-thirty-four children with melioidosis were treated with trimethoprim-sulfamethoxazole for 3 to 6 months. This treatment caused adverse-effects and a change of treatment or a reduction of the dose necessitated in some children. Of these children, 16 (6.8%) died during treatment and 6 children (2.6%) did not complete the therapy because the adverse-effects [8]. Trimethoprim-sulfamethoxazole was administered to 99 children with intestinal infection caused by Enterobacteriaceae. Initially, trimethoprim-sulfamethoxazole usage was strongly associated with appearance of an integron-positive multidrug-resistant Enterobacteriaceae in the intestinal flora. After prolonged exposure to this drug combination the population of Enterobacteriaceae was substituted by a population with non-integron-associated resistance-mechanisms and

after trimethoprim-sulfamethoxazole was discontinued the susceptibility-rate returned to baseline level [9]. Following the administration of trimethoprim-sulfamethoxazole to children the treatment caused cutaneous toxicity (from 1.4 to 7.4% of children), haematological toxicity (from 0 to 72.1% of children), and hepatotoxicity (in 5.0% of children) but serious adverse-effects are extremely rare and are reversible by discontinuance of therapy [10]. The development of haematological abnormalities was evaluated in 50 children who were treated with trimethoprim-sulfamethoxazole. Neutropenia occurred in 34.0% of children and thrombocytopenia developed in 12.0% of children. Neutropenia lasted for 9 days and thrombocytopenia was noted for 13 days and these adverse-effects disappeared after the cessation of treatment [11].

Pharmacokinetics of trimethoprim and sulfamethoxazole in infants and children

Autmizguine et al. [12] studied the pharmacokinetics of trimethoprim and sulfamethoxazole in 153 infants and children with median postmenstrual age, postnatal age, and body-weight of 38 weeks, (range, 32 to 39), 7.9 years (range, 0.1 to 20.2), and 30.8 kg (range, 2.4 to 148), respectively. One-hundred-nine subjects (71.2%) were white, 29 (19.0%) were black 3, and 12 (7.8%) were of other origins. The subject ethnicity was Hispanic 26 (17.0%), not Hispanic 123 (80.3%), and 4 (2.6%) of unknown ethnicity. The median dose of trimethoprim and sulfamethoxazole was 2.5 mg/kg per dose (range, 0.5 to 12.1) and 12.7 mg/kg per dose (range, 2.5 to 60.2), respectively. The median daily dose of trimethoprim and sulfamethoxazole was 4.6 mg (range, 2.5 to 60.2) and 23.0 mg (range, 2.5 to 120), respectively. The median dose interval was 12 hours (range, 6 to 48). Seventy-eight subjects (50.9%) received an oral suspension of trimethoprim-sulfamethoxazole of 8/40 mg/ml at the time of the first recorded dose, while the remaining subjects received trimethoprim-sulfamethoxazole tablets of 80/400 mg or 160/800 mg. Dosing was via the oral route in 125 subjects (81.7%), via a gastrostomy tube 17 subjects (11.1%), and by other routes in 11 subjects (7.2%).

	Final model		Bootstrap analysis (N = 1,000)		
Parameter	Estimate	%RSE	2.5th percentile	Median	97.5th percentile
Ka (h^{-1})	1.27	35.8	0.6	1.27	2.4
TBC/F_{70kg} (L/h)	10.0	5.5	8.8	9.9	11.0
DV/F_{70kg} (L)	148	6.8	129	148	173
TM_{50} (years)	0.24	24.8	0.14	0.24	0.40
Hill	1 (fixed)	---	---	---	---
Exponent for SCR effect on TBC/F					
IIV (TBC/F) (%CV)	33.8	36.8	10.0	31.6	44.7
IIV (DV/F) (%CV)	20.6	89.2	4.7	22.3	50.1
Proportional error (%)	51.1	4.4	42.3	50.0	57.6

RSE = relative standard error. Ka = absorption-rate constant. TBC/F_{70kg} = Total body clearance scaled to a 70 kg adult. DV/F_{70kg} = distribution volume scaled to 70 kg adult. TM_{50} = maturation elimination half-life calculated as a function of postnatal age (in years). SCR = serum creatinine concentration. IIV (TBC/F) = interindividual variability of total body clearance. IIV (DV/F) = interindividual variability of distribution volume. %CV = %coefficient of variation. F = bioavailability.

Table 1: *Pharmacokinetic parameters of trimethoprim which are obtained in 153 infants and children, by Autmizguine et al. [12]*

This table shows that trimethoprim is rapidly absorbed following oral administration as the absorption-rate constant is 1.27 h^{-1}, trimethoprim is distributed in a volume larger than the water volume, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the variation in the subject demographic characteristics.

	Median and (range) for the following age groups			
	0 to < 2 years (N = 46)	2 to < 6 years (N = 25)	6 to < 21 years (N = 82)	Total (N = 153)
Parameter				
TBC/F (L/h/kg)	0.20 (0.05 – 0.44)	0.23 (0.14 – 0.43)	0.14 (0.04 – 0.31)	0.16 (0.04 – 0.44)
TBC (L/h/70 kg)	9.6 (1.5 – 18.1)	11.4 (6.2 – 21.4)	9.3 (2.5 – 18.0)	9.6 (1.5 – 21.4)
DV (L/kg)	2.1 (1.8 – 2.5)	2.1 (1.8 – 2.4)	2.1 (1.4 – 2.4)	2.1 (1.4 – 2.5)
DV (L/70 kg)	149 (125 – 175)	149 (127 – 171)	147 (96 – 168)	148 (96.2 175)
Elimination half-life (h)	5.9 (3.3 – 33.2)	6.5 (3.1 – 11.3)	11.1 (4.3 – 32.6)	8.7 (3.1 -33.2)

TBC = total body clearance. DV = distribution volume. F = bioavailability.

Table 2: *Trimethoprim individual empirical Bayesian post hoc parameter estimates which are stratified by age in 153 infants and children. Values are the median and range, by Autmizguine et al. [12].*

This table shows that the total body clearance and the distribution volume are independent by the subject age, the elimination half-life increases with the infant maturation and child development, there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the variation in subject age.

	Final model		Bootstrap analysis (N = 1,000)		
Parameter	Estimate	%RSE	2.5th percentile	Median	97.5th percentile
Ka (h^{-1})	0.58	43.9	0.1	0.60	1.3
TBC/F_{70kg} (L/h)	1.46	5.1	1.30	1.45	1.76
DV/F_{70kg} (L)	24	10.0	6	23	29
TM_{50} (years)	0.12	16.4	0.05	0.13	0.17
Hill	2.13	59.6	0.3	2.3	11.4
Exponent for ALB effect on TBC/F					
IIV (TBC/F (%)	35.9	46.2	9.2	33.2	51.3
IIV DV/F) (%)	40.6	41.1	18.3	39.6	114
P (TBC/F – DV/F)	0.1	56.7	-0.1	0.1	0.3
Proportional error (%)	46.9	16.7	34.7	45.8	53.4

Additive error (mg/L)	5.1	38.0	1.8	5.5	322

Ka = absorption-rate constant. RSE = relative standard error. TBC/F_{70kg} = total body clearance scaled to a 70 kg adult. DV/F_{70kg} = distribution volume scaled to 70 kg adult. TM_{50} = maturation elimination half-life calculated as a function of postnatal age (in years). Hill = Hill coefficient in the Emax maturation function. ALB = serum albumin concentration. SRC = serum creatinine concentration. IIV (TBC/F) = interindividual variability of total body clearance. IIV(DV/F) = interindividual variability of the distribution volume. P (TBC/F – DV/F) = correlation between random effect parameters for TBC/F and DV/F. F = bioavailability

Table 3: *Pharmacokinetic parameters of sulfamethoxazole which have been obtained in 153 infants and children, by Autmizguine et al. [12].*

This table shows that the absorption-rate constant, the total body clearance, and the distribution volume of sulfamethoxazole are smaller than those of trimethoprim and there is a remarkable interindividual variability in the pharmacokinetic parameters and this variability is accounted by the variation in subject demographic characteristics.

		AUC0-Γ,ss (mg*h/L) data are the median and (2.5^{th} - 97.5^{th} percentile)					
		Oral dosing twice-daily		Oral dosing thrice-daily		Oral dosing 4 times-daily	
Age group	N. subjects	8 mg/kg/day[a]	12 mg/kg/day[b]	15 mg/kg/day[c]	20 mg/kg/day[d]	15 mg/kg/day[e]	20 mg/kg/day[f]
0 to < 2 years	500	19.2 (9.2 – 59.1)	28.7 (13.8 – 88.7)	23.0 (11.5 – 73.9)	32.1 (15.4 – 99.0)	17.9 (8.6 – 55.4)	23.9 (11.5 – 73.8)
2 to < 6 years	500	19.0 (9.8 – 35.9)	28.5 (14.7 – 53.8)	23.8 (12.2 – 44.9)	31.8 (16.4 – 60.1)	17.8 (9.2 – 33.6)	23.8 (12.2 – 44.9)
6 to 21 years	1,500	22.8 (11.4 – 45.7)	36.2 (18.0 – 76.5)	30.7 (15.7 – 63.7)	41.0 (21.0 – 85.4)	23.1 (11.8 - 479)	30.7 (15.7 – 63.7)
18 to 21 years	500	19.5 (10.2 – 39.5	39.1 (20.3 – 79.0)	42.8 (22.2 – 86.4)	57.3 (27.7 - 116)	32.1 (16.6 – 64.8)	42.8 (22.2 – 86.4)

AUC0-Γ, ss = AUC at steady-state from 0 to Γ (where Γ denotes the dosing interval). [a]Maximum daily dose 320 mg (1 double-strength tablet every 12 hours) achieved at a body-weight of 40 kg. [b]Maximum daily dose 640 mg (2 double-strength tablets every 12 hours) achieved at a body-weight of 53 kg. [c]Maxumum daily dose 1,200 mg (2 double-strength tables + 1 single-strength tablet every 8 hours) achieved at a body-weight of 60 kg. [d]Maximum daily dose 1,440 mg (3 double-strength tablets every 8 hours) achieved at a body-weight of 85 kg. [e]Maximum daily dose 1,200 mg (2 double-strength tablets every 6 hours) achieved at a body-weight of 85 kg. [f]Maximum daily dose 1,600 mg (2 double-strength tablets + 1 single-strength tablets every 6 hours) achieved at a body-weight of 80 kg.

Table 4: *Simulated trimethoprim exposure at steady stale. Values are the median and (range), by Autmizguine et al. [12]*

This table shows that the estimates of the area under the concentration-time curve of trimethoprim obtained at the age group of 0 to < 2 years are generally lower than those obtained at the age group of 18 to 21 years.

Inhibition of cytochromes P-450 (CYP) by trimethoprim or by sulfamethoxazole

It was evaluated the inhibitory effects of trimethoprim and sulfamethoxazole on recombinant CYP2C8 and CYP2C9. With concentrations ranging from 5 to 100 µM, trimethoprim exhibits a selective inhibitory effect on CYP2C8-mediated paclitaxel 6-alpha-hydroxylation in human liver microsomes and recombinant CYP2C8, with apparent IC_{50} (Ki) values of 54 µM and 75 µM, respectively. With concentrations ranging from 50 to 500 µM, sulfamethoxazole was a selective inhibitor of CYP2C9-mediated tolbutamide hydroxylation in human liver microsomes and recombinant CYP2C9, with apparent IC_{50} (Ki) values of 544 µM, and 456 µM, respectively. In conclusion, trimethoprim and sulfamethoxazole can be used as selective inhibitors of CYP2C8 and CYP2C9, respectively [13].

Interaction of trimethoprim-sulfamethoxazole with drugs

Trimethoprim-sulfamethoxazole interacts with warfarin and induces bleeding [14] and concurrent use of vitamin K and trimethoprim-sulfamethoxazole causes blending [15]. Methotrexate and trimethoprim-sulfamethoxazole combination causes extremely serious and life-threatening effects and this drug association should be avoided [16]. Trimethoprim is a potent inhibitor of the renal tubular secretion and can increase plasma concentrations of amantadine, dapsone, digoxin, dofetilide, lamivudine, methotrexate, procainamide, and zidovudine. Trimethoprim can also inhibit sodium channels of the renal distal tubules and may cause hyperkalaemia when it is co-administered with angiotensin-converting enzyme inhibitors. In addition, hyponatremia has been associated with the co-administration of thiazide diuretics and trimethoprim therapy [17].

Prophylaxis with trimethoprim-sulfamethoxazole

Six-hundred-seven infants and children, aged 12 months (range, 2 to 71), were treated with trimethoprim-sulfamethoxazole for 2 years and anthropometric data were completed at 24 months of follow-up in 214 subjects who received the therapy and in 214 subjects who received placebo. Analysis of data revealed that the prophylaxis with this antibiotic does not cause increase of body-weight, prevalence of overweight, or obesity [18]. Short-term prophylaxis with trimethoprim-sulfamethoxazole is effective in controlling Pneumocystis jirovecii infection and preventing future outbreaks of Pneumocystis pneumonia among subjects with rheumatoid arthritis [19]. Prophylaxis with prolonged trimethoprim-sulfamethoxazole prevents Plasmodium falciparum malaria in HIV-exposed children aged up to age 4 years [20]. Long-term prophylaxis with low-dose of trimethoprim-sulfamethoxazole was associated with a decreased number of urinary-tract infections in children [21]. Prophylaxis with trimethoprim-sulfamethoxazole prevents urinary-tract infection in infants and children [22]. Prophylaxis with trimethoprim-sulfamethoxazole effectively prevents Plasmodium falciparum malaria infection and disease and does not select parasites resistant to trimethoprim-sulfamethoxazole [23].

Treatment of bacterial infections with trimethoprim-sulfamethoxazole in infants and children

Trimethoprim-sulfamethoxazole effectively treats Flavobacterium meningosepticum sepsis in infants because of its activity against this organism and the good penetration into the brain [24]. Trimethoprim-sulfamethoxazole treats children infected by Pneumocystis carinii and also treats children with pulmonary and disseminated nocardiosis and some forms of Wegener's granulomatosis [25]. Trimethoprim and sulfamethoxazole were administered by an intravenous infusion at doses of 5 and 25 mg/kg, respectively, 4 times-daily to 11 infants and children, aged 3 weeks to 13 years, suffering from serious infection caused by Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, or by Acinetobacter anitratus and this treatment cured the infections [26]. Trimethoprim-sulfamethoxazole was administered orally for 3 to 4 days to children, aged 10 months to 15 years, suffering from the infection causes by Salmonella gastroenteritis and this treatment cured the infection [27].

Treatment of bacterial meningitis with trimethoprim-sulfamethoxazole and penetration of trimethoprim and sulfamethoxazole into the cerebrospinal fluid (CSF)

An infant aged 7 month had meningitis caused by Listeria monocytogenes which did not respond to ampicillin and to an aminoglycoside whereas

the meningitis was cured with trimethoprim-sulfamethoxazole which was administrate for 3 weeks [28]. An extremely premature infant had the meningitis caused by Elizabethkingia meningoseptica and the meningitis was cured with trimethoprim-sulfamethoxazole [29]. A patient with Nocardia meningitis was treated with trimethoprim-sulfamethoxazole and the meningitis was cured [30]. A single intravenous infusion of 5 mg of trimethoprim and 25 mg of sulfamethoxazole was administered to patients. The peak concentration of trimethoprim and sulfamethoxazole occurred 60 and 480 min, respectively, after the infusion. In the post-infusion phase, the concentration of trimethoprim in the CSF and serum was 0.23 and 0.53 µg/ml, respectively, and that of sulfamethoxazole was 0.20 and 0.36 µg/ml, respectively [31]. Two patients had meningitis caused by Staphylococcus aureus and 4 patients had meningitis due to Listeria monocytogenes and meningitis was cured with trimethoprim-sulfamethoxazole in all patients [32]. Trimethoprim was administered orally and intravenously to patients and trimethoprim penetrates into the CSF in significant amounts even when the meninges are not inflamed [33].

Transfer of trimethoprim and sulfamethoxazole across the human placenta

In literature there is only one study on the transfer of trimethoprim and sulfamethoxazole across the human placenta and has been reported by Bawdon et al. [34]. The placental transfer of trimethoprim and sulfamethoxazole was studied using the perfusion of the placenta. The concentration of trimethoprim in the maternal and foetal compartments was 7.2 µg/ml and 1.4 µg/ml, respectively, at 1 hour of perfusion. When the concentration of trimethoprim was 1.0 µg/ml in the maternal compartment the concentration of trimethoprim in the foetal compartment was 0.08 µg/ml. The concentration of sulfamethoxazole in the maternal and foetal compartments ranged from 29.6 to 127.7 µg/ml and from 5.1 to 14.8 µg/ml, respectively. These results indicate that trimethoprim and sulfamethoxazole are poorly transferred across the human placenta.

Migration of trimethoprim and sulfamethoxazole into the breast-milk

Fourteen lactating women received trimethoprim orally at a daily dose of 320 mg and the peak and trough concentrations of trimethoprim in the milk averaged to 2.4 µg/ml and to 1 µg/ml, respectively. Other 6 lactating women received trimethoprim orally at a daily dosage of 480 mg and the peak and trough concentrations of trimethoprim in the milk averaged to 4 and 1.5 µg/ml, respectively. These results indicate that trimethoprim poorly migrates into the breast-milk [35]. Forty lactating women received co-trimoxazole twice-daily orally equivalent to 800 mg of sulfamethoxazole and 320 mg of trimethoprim. After 5 days of therapy, the concentration of trimethoprim and sulfamethoxazole averaged to 2.0 and 4.5 µg/ml, respectively [36]. These results indicate that trimethoprim and sulfamethoxazole poorly migrate into the beast-milk.

Discussion

Cell growth and proliferation after nanofibrous scaffold implantation

Trimethoprim-sulfamethoxazole is the sulphonamide used in paediatric patients. Trimethoprim-sulfamethoxazole is a useful antimicrobial drug but must be used when other antibiotics such as penicillins and cephalosporins cannot be employed. Trimethoprim inhibits bacterial dihydrofolate reductase an enzyme downstream form the one that sulphonamides inhibit in the same biosynthetic sequence. The combination of trimethoprim with sulfamethoxazole is an important advance in the development of clinically effective and synergistic antimicrobial agents. Trimethoprim-sulfamethoxazole is available in a single-entity preparation and is also known as co-trimoxazole. The antimicrobial activity of the combination of trimethoprim with sulfamethoxazole results from actions on sequential steps of the activity pathway for the synthesis of tetrahydrofolic acid. Tetrahydrofolate is essential for one-carbon transfer reactions (e.g., the synthesis of thymidylate from deoxyuridylate). Mammalian cells use preformed folates from the diet and do not synthesize these compounds. The optimal ratio of the combinations of the two agents equals the ratio of the MICs of the drugs acting independently and this ratio is 20:1 sulfamethoxazole: trimethoprin. Although each agent alone usually exerts bacteriostatic activity when the organism is sensitive to both agents bactericidal activity may be achieved. Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermis, Streptococcus pyogenes, the viridians group of streptococci, Escherichia coli, Proteus mirabilis, Klebsiella species, Enterobacter species, Salmonella, Pseudomonas pseudomallei, Serratia, Alcaligenes species, Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Yersinia enterocolitica, and Nocardia asteroides are susceptible to trimethoprim-sulfamethoxazole [1]. The oral dose of co-trimoxazole is 120 mg twice-daily in infants and 240, 480, and 960 mg twice-daily in children aged up to 5 years, 6 to 11, and 12 to 17 years, respectively [2]. The efficacy and safely of trimethoprim-sulfamethoxazole have been reviewed. Trimethoprim-sulfamethoxazole effectively and safely treats Plasmodium falciparum malaria in children and the prophylaxis with trimethoprim-sulfamethoxazole prevents Plasmodium falciparum malaria in children [3], prolonged treatment with trimethoprim-sulfamethoxazole effectively and safely treats osteomyelitis in children [4], trimethoprim-sulfamethoxazole effectively and safely treats urinary-tract infection in children [5], urinary-tract infection, vesico-ureteric reflux, and renal scarring in children [6], and pneumonitis caused by Pneumocystis carinii in children [7]. These results indicate that trimethoprim-sulfamethoxazole effectively and safely treats infections caused by different organisms in children. The adverse-effects caused by trimethoprim-sulfamethoxazole have been reviewed. Two-hundred-thirty-four children were treated with trimethoprim-sulfamethoxazole for 3 to 6 months for melioidosis, 16 children (6.8%) died during treatment and 6 children (2.6%) did not complete the therapy because the adverse-effects [8]. Trimethoprim-sulfamethoxazole was administered to 99 children. Initially trimethoprim-sulfamethoxazole was strongly associated with the appearance of integron-positive drug-resistant to Enterobacteriaceae in the intestinal flora. After prolonged exposure to trimethoprim-sulfamethoxazole, however, this population of Enterobacteriaceae was substituted by a population with non-integron-associated resistance mechanisms. After trimethoprim-sulfamethoxazole was discontinued, susceptibility rates to all antibiotics returned to baseline levels [9]. Trimethoprim-sulfamethoxazole causes cutaneous toxicity, haematological toxicity, or hepatotoxicity in some children but the serious adverse-effects are rare and are reversible by discontinuation of therapy [10]. Trimethoprim-sulfamethoxazole causes neutropenia or thrombocytopenia in some children but the adverse-effects disappears after the cessation of treatment [11]. These results indicate that trimethoprim-sulfamethoxazole may cause adverse-effects, the adverse-effects may be serious, but in general disappear with the discontinuous of treatment. The pharmacokinetics of trimethoprim and sulfamethoxazole have been studied by Autmizguine et al. [12] in infants and children who received trimethoprim-sulfamethoxazole orally. Both trimethoprim and sulfamethoxazole are rapidly absorbed with an absorption-rate constant of 1.27 and 0.58 h-1, respectively. In infants and children with a body-weight ranging from 2.4 to 148 kg the total body clearance is 10.0 and 1.46 L/h, scaled to 70 kg, for trimethoprim and sulfamethoxazole, respectively, indicating that trimethoprim is more effectively cleared than sulfamethoxazole. The distribution volume of trimethoprim and sulfamethoxazole, scaled to 70 kg, is 148 and 24 L, respectively, indicating that trimethoprim is distributed in a larger volume than sulfamethoxazole. The elimination half-life of trimethoprim ranges from 5.9 to 11.1 hours and increases with infant maturation and child development. The inhibition of cytochrome P-450 (CYP) by trimethoprim and by sulfamethoxazole has been studied and trimethoprim and sulfamethoxazole are potent inhibitors of CYP2C8 and CYP2C9, respectively [13]. The interaction of trimethoprim-sulfamethoxazole with drugs has been reviewed. The interaction of trimethoprim-sulfamethoxazole with warfarin [14] or with vitamin K [15] induces

blending, and the interaction of trimethoprim-sulfamethoxazole with methotrexate induces life-threatening effects [16]. Trimethoprim is a potent inhibitor of the renal tubular secretion and increases the plasma concentration of different drugs. Trimethoprim inhibits sodium channels of the renal distal tubules and may cause hyperkalaemia when it is co-administered with angiotensin-converting enzyme inhibitors. In addition, the co-administration of trimethoprim with thiazine diuretics causes hyponatremia [17]. These results indicate that trimethoprim-sulfamethoxazole interacts with drugs and the interaction may cause serious adverse-effects. The prophylaxis with trimethoprim-sulfamethoxazole has been reviewed. Prophylaxis with trimethoprim-sulfamethoxazole performed for 2 years does not increase body-weight or obesity in children [18], short-term prophylaxis with trimethoprim-sulfamethoxazole controls Pneumocystis jirovecii infection and prevents Pneumocystis pneumonia in subjects with rheumatoid arthritis [19], and the prophylaxis with prolonged trimethoprim-sulfamethoxazole prevents Plasmodium falciparum malaria in HIV-exposed children [20]. Long-term prophylaxis with low dose of trimethoprim-sulfamethoxazole prevents urinary-tract infection in children [21], the prophylaxis with trimethoprim-sulfamethoxazole prevents urinary-tract infection in infants and children [22], and prevents Plasmodium falciparum malaria and does not select parasites resistant to trimethoprim-sulfamethoxazole [23]. These results indicate that the prophylaxis with trimethoprim-sulfamethoxazole does not increase body-weight or obesity in children and prevents urinary-tract infection and Plasmodium falciparum malaria in children. The treatment of bacterial infections with trimethoprim-sulfamethoxazole has been reviewed. Trimethoprim-sulfamethoxazole treats the sepsis caused by Flavobacterium meningosepticum in infants [24], the infection caused by Pneumocystis carinii, disseminated nocardiosis, and Wegener's granulomatosis in children [25], serious infections caused by Haemophilus influenzae, Streptococcus pneumonia, Streptococcus pyogenes, or by Acinetobacter anitratus in infants and children [26], and treats children infected by Salmonella gastroenteritis [27]. These results indicate that trimethoprim-sulfamethoxazole treats the infection caused by different organisms in infants and children. The treatment of bacterial meningitis with trimethoprim-sulfamethoxazole and the penetration of trimethoprim and sulfamethoxazole into the cerebrospinal fluid have been reviewed. Trimethoprim-sulfamethoxazole administered for 3 weeks treats the meningitis caused by Listeria monocytogenes in infants [28], trimethoprim-sulfamethoxazole treats the meningitis caused by Elizabethkingia meningoseptica in an infant [29], and the meningitis caused by Nocardia meningitis in a patient [30]. Following a single intravenous infusion of 5 mg of trimethoprim and 25 mg of sulfamethoxazole the peak concentration of trimethoprim and sulfamethoxazole occur 60 and 480 min, respectively, after the infusion. In the post-infusion phase, the concentration of trimethoprim in the cerebrospinal fluid and in serum is 0.23 and 0.53 µg/ml, respectively, and that of sulfamethoxazole is 0.26 and 0.36 µg/ml, respectively [31]. Trimethoprim-sulfamethoxazole treats the meningitis caused by Staphylococcus aureus or by Listeria monocytogenes in patients [32], and trimethoprim administered intravenously to patients penetrate into the cerebrospinal fluid in significant amounts even when the meninges are not inflamed [33]. These results indicate that trimethoprim-sulfamethoxazole treats the meningitis caused by different bacteria and trimethoprim and sulfamethoxazole penetrate into the cerebrospinal fluid in significant amounts. The transfer of trimethoprim and sulfamethoxazole across the human placenta has been studied using the perfusion of the placenta and both trimethoprim and sulfamethoxazole are poorly transferred across the human placenta [34]. The migration of trimethoprim and sulfamethoxazole into the breast-milk has been assessed in two studies [35, 36] and both trimethoprim and sulfamethoxazole poorly migrate into the breast-milk.

Conclusion

In conclusion, trimethoprim-sulfamethoxazole is the sulphonamide used in paediatric patients. Trimethoprim-sulfamethoxazole, also known as co-trimoxazole, is a useful antimicrobial drug but must be used when other antibiotics such as penicillins and cephalosporins cannot be employed. Co-trimoxazole is administered at an oral dose of 120 mg twice-daily to infants and at an oral dose of 240, 480, and 960 mg twice-daily to children aged up to 5 years, 6 to 11 years, and 12 to 17 years, respectively. Following the oral administration, trimethoprim and sulfamethoxazole are rapidly absorbed with an absorption-rate constant is 1.27 and 0.58 h-1, respectively. Trimethoprim-sulfamethoxazole has been found efficacy and safe in children but may induce adverse-effects. Trimethoprim-sulfamethoxazole interacts with drugs and the prophylaxis with trimethoprim-sulfamethoxazole prevents bacterial infections and the treatment with this drug combination treats infections caused by different bacteria. Trimethoprim-sulfamethoxazole treats the meningitis caused by different bacteria and trimethoprim and sulfamethoxazole penetrate into the cerebral spinal fluid in significant amounts. Trimethoprim and sulfamethoxazole are poorly transferred across the human placenta and poorly migrate into the breast-milk. The aim of this study is to describe the clinical pharmacology of trimethoprim-sulfamethoxazole in paediatric patients.

Conflicts of Interest

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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